

Medical



Journal



JODIE JENKINSON

- Diabetes Mellitus
- Vertigo
- Spondylolisthesis
- Prostate Specific Antigen
- Emergency Ultrasonography
- D2 Receptor
- MS and Myasthenia Gravis
- Obstetrics and Gynecology Rounds



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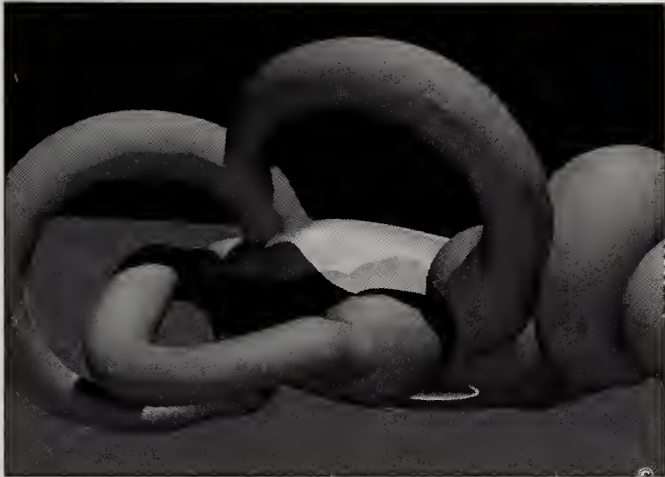
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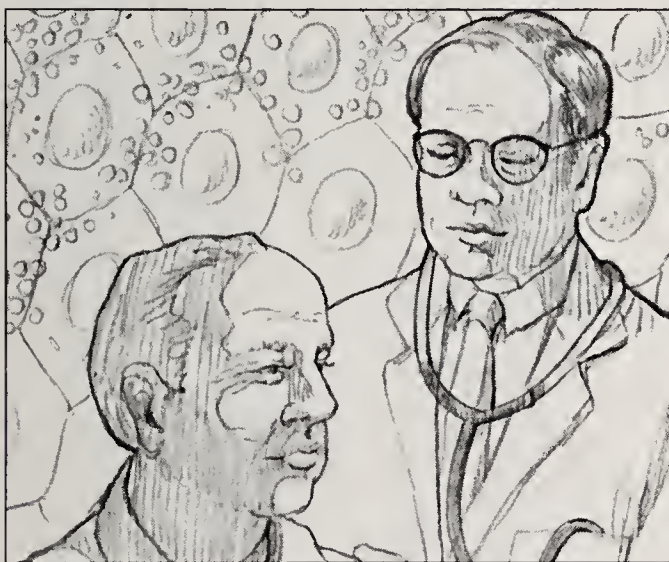


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Editorial

In this, the second edition of volume #73 of the University of Toronto Medical Journal, we present an eclectic collection of original research from both the clinical and basic sciences. In addition, we are fortunate to have the opportunity to publish a number of submissions concerning issues that are particularly current in both the scientific and political medical arenas.

In our *News* section, we have provided readers with an account of the recent and successful Medical Student Research Day, which is an annual testament to the diversity and high quality of the medical research that is generated at U of T.

The recent passage of Bill 26, *The Savings and Restructuring Act*, has instigated widespread debate in the medical community and has engendered feelings of ambivalence among many doctors and future doctors toward the notion of practicing medicine in Ontario. This is reflected in the selection of essays that we present in our *Views* section. The various authors examine the considerable ramifications of the Bill with respect to the provision of quality health care services in this province. The implications for medical students and residents are equally profound as new physicians will face unprecedented impediments to receiving fair remuneration for their services and to practicing medicine in the communities of their choice. It is the hope of the Editors that Journal readers will respond to the articles published here, and that our editorial section can serve as a forum for discourse on this or any other topic relating to medical science.

As we approach the 75th anniversary of Banting and Best's discovery of insulin, it is timely to reflect on the historical significance of diabetes and on the progress that has been made in our knowledge of this condition. Diabetes has been known to medical science for millennia. Early references to a condition resembling diabetes are found in Egyptian inscriptions that likely represent the medical ideas of five to six thousand years ago. Diabetes is similarly alluded to in ancient Chinese manuscripts. Medical texts from India expound ideas dating from as far back as the 7th century B.C.E. and indicate that Indian medicine recognized the then poor prognosis for diabetics and identified the sweet taste of diabetic urine well before it became known to the Europeans in the 17th century.¹ Writings of the ancient Greeks from the 2nd century A.D. demonstrate a familiarity with the natural history of the disease. The noted Greek physician Aretaeus described diabetes in this way:

...a melting down of the flesh and limbs into urine....for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts....The nature of the disease then is chronic... but the patient is short-lived if the constitution of the disease be completely established.²

His description of the symptomatology is equally vivid: "Moreover, life is disgusting and painful; thirst unquenchable...their mouth becomes parched and their body dry..."² Mercifully, diabetics now face a significantly improved prognosis thanks to the discovery of insulin by Banting and Best at U of T in 1922. In our *Looking Back* section, we reprint an article submitted by them in 1924. This is complemented by our *Commentary* section in which Dr. Anthony Sun describes recent, exciting advancements in the area of bioengineered tissue to replace damaged pancreatic islets, a technique which may represent the end of diabetes as a major health risk.

Finally, the UTMJ would like to welcome the Bank of Montreal as the new sponsor of the *Quick Diagnosis* section. It is through their support and the support of all our private patrons that the Journal is able to exist and that we are able to continually improve the UTMJ as a showcase for the research and intellectual discourse that exists at U of T.

Mark J. Korman
Mary K. Nagai

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1996 University of Toronto Medical Student Research Day

Mary Kikumi Nagai, Ph.D. (9T8)

On January 9, 1996, the Faculty of Medicine at the University of Toronto held its annual Medical Student Research Day at the Medical Sciences Building. This event serves as a forum for medical students to share their research ideas with each other and with the university community.

Sixty three posters were presented and the following students were awarded George Brown Memorial Awards:

Novice Researcher (Basic or Clinical) Category

MARC OSSIP (2nd year medical student)

Supervised by Michael Wood, Department of Medical Imaging

Reducing noise in functional MRI by aligning images prior to brain activation mapping.

KAMRAN AHMAD (2nd year medical student)

Supervised by David S. Riddick, Department of Pharmacology

The role of glutathione S-transferase isozymes in the resistance of human colon cancer cell lines to doxorubicin.

Experienced Researcher (Basic) Category

MICHAEL HEIBER (2nd year medical student)

Supervised by Brian O'Dowd, Department of Pharmacology

Cloning and characterization of a human gene encoding a novel G protein-coupled receptor.

In addition, Michael Heiber will receive financial support to present his work at the 37th Annual National Student Research Forum at the University of Texas, Medical Branch at Galveston in Spring 1996.

Experienced Researcher (Clinical) Category

KOSTAS PANAGIOTOPOULOS and **ROBERT MASNYK** (3rd year medical students)

Supervised by Allan Gross, Department of Surgery

Dislocation following total hip revision with allograft.

MD/Ph.D. Student Researcher (Basic or Clinical) Category

ALLY-KHAN SOMANI

Supervised by Kathy Siminovitch, Department of Medicine

The PTP1C protein tyrosine phosphatase regulates the catalytic activity of the proto-oncogenic src protein tyrosine kinase.

In addition, Ally-Khan Somani will receive financial support to present his work at the 37th Annual National Student Research Forum at the University of Texas, Medical Branch at Galveston in Spring 1996.

Department of Medicine Award

ERIC CHU (2nd year medical student)

Supervised by Art Slutsky, Department of Medicine

The effects of the stress response in a rat model of sepsis.

Eric Chu will receive financial support from the Department of Medicine to present his work at the 37th Annual National Student Research Forum at the University of Texas, Medical Branch at Galveston in Spring 1996.

The winning abstracts are printed on the following pages. Congratulations to all of the 1996 award winners!

Novice Researcher (Basic or Clinical) Category

REDUCING NOISE IN FUNCTIONAL MRI BY ALIGNING IMAGES PRIOR TO BRAIN ACTIVATION MAPPING. M. G. Ossip*, A. Kassam, and M. Wood. Dept. of Medical Imaging, Faculty of Med., Univ. of Toronto, Toronto, M5B 1W8.

Functional magnetic resonance imaging (fMRI) provides information associated with brain activation. Images of a particular anatomical slice are acquired repetitively under the presence of a stimulus and under control conditions. Typical stimuli include vision, smell and pain. According to an established model, the activated regions of the brain are brighter in the images acquired during presentation of the stimulus. Various statistical methods are used to bring out the slight intensity differences. Statistical processing produces an activation map of the brain in which brighter pixels represent activated regions. This processing assumes that the differences between images are due only to brain activation. The main difficulty in fMRI is that any movement during image acquisition creates differences between images due to anatomical misalignment and not brain activation.

The hypothesis was that aligning images prior to statistical processing reduces extraneous variation caused by misalignment, resulting in activation maps containing less noise. The functional magnetic resonance (fmr) images used were acquired by previous investigators. In order to verify that these images were misaligned, they were rapidly displayed in sequential order producing an animation which demonstrated movement. Additionally, the differences between images was quantified confirming the movement observed in the animation. An algorithm was developed to align the images, and it successfully detected and corrected sets of purposely misaligned images. The uncorrected fmr images were processed resulting in brain activation maps obscured by noise. The fmr images were then aligned using the algorithm and reprocessed, resulting in brain activation maps with markedly reduced noise.

These experiments confirmed that misaligned fmr images are routinely obtained in practice, and that aligning them prior to processing produces activation maps which better represent stimulus induced brain activation.

Novice Researcher (Basic or Clinical) Category

THE ROLE OF GLUTATHIONE S-TRANSFERASE ISOZYMES IN THE RESISTANCE OF HUMAN COLON CANCER CELL LINES TO DOXORUBICIN K. Ahmad*, P.O. Beaumont, M.J. Moore and D.S. Riddick. Depts. of Pharmacology and Medicine, University of Toronto, Toronto, ON., M5S 1A8

Colorectal cancer is the second leading cause of cancer deaths in North America due, in part, to a high incidence of intrinsic drug resistance. Doxorubicin, a commonly used anthracycline, is effective in many types of cancer but has little activity against colorectal cancers. It is hypothesized that this is due to a multifactorial resistance mechanism in which the glutathione S-transferase (GST)-glutathione (GSH) enzyme-cofactor system plays a role. Our objective was to examine the relationship between GST isozyme expression and doxorubicin resistance in four human colon adenocarcinoma cell lines (CaCo-2, LoVo, HT-29 and SW620), so as to provide a basis for studies of drug resistance modulation by GST inhibitors. GST catalytic activity was measured by spectrophotometric assay, using general and isozyme-selective substrates, and GST protein expression was assessed by immunoblot. The sensitivity of the cell lines to doxorubicin was determined using a microplate colorimetric cytotoxicity assay.

Total GST activity was measured as the rate of conjugation of 1-chloro-2,4-dinitrobenzene (CDNB) with GSH and was significantly higher in CaCo-2 cells ($p < 0.001$) as compared to the other cell lines. The four cell lines did not differ in GST- π immunoreactive protein or GST- π selective catalytic activity as assessed by ethacrynic acid-GSH conjugation. Preliminary results also show a unique GST- α immunoreactive band in CaCo-2 cells, not present in the other cell lines. CaCo-2 cells were most resistant to doxorubicin, showing an IC_{50} value approximately 10-fold higher than LoVo and HT-29 and 100-fold higher than SW620.

These results will help to elucidate the relationship between GST expression and drug resistance, as well as directing ongoing studies in modulating doxorubicin resistance with the use of isozyme-selective GST inhibitors. The ultimate goal of this project is to conduct clinical trials of doxorubicin with a GST enzyme inhibitor in colorectal cancer patients.

Experienced Researcher (Basic) Category

CLONING AND CHARACTERIZATION OF A HUMAN GENE ENCODING A NOVEL G PROTEIN-COUPLED RECEPTOR Michael Heiber*, Adriano Marchese, Tuan Nguyen, Susan R. George and Brian F. O'Dowd. Department of Pharmacology, University of Toronto

The elucidation of the molecular mechanisms underlying the functioning of the endocrine system is proceeding at a rapid rate. This has been facilitated by the cloning and characterization of the genes encoding a number of different hormones and receptors, permitting the detailed pharmacological and biochemical analysis of these proteins. During this undertaking, it was observed that the structure of many different hormone receptor proteins are very similar. The most salient features include 7 transmembrane domains and numerous conserved amino acids. These receptors have been grouped into one large superfamily called G protein-coupled receptors (GPCR).

We sought to identify novel hormone receptors by cloning and characterizing the respective genes. We proceeded by designing degenerate oligonucleotide primers based on conserved regions in genes encoding previously cloned GPCRs. These primers were used in the polymerase chain reaction (PCR) to amplify human genomic DNA. This resulted in the identification of one unique PCR product, which was subsequently used as a probe to screen a human genomic DNA library. Seven probe-binding phage clones from this library were purified and the inserts were characterized by Southern blot analysis. A 1700 bp fragment from one of the phage clones was subcloned and the insert was sequenced and found to contain the complete coding region of a novel gene we have named GPR15.

Analysis of the translated amino acid sequence of GPR15 revealed 7 hydrophobic regions corresponding to 7 transmembrane domains as well as the highly conserved DRY sequence in the second intracellular loop. In addition, the amino acid sequence of GPR15 shares sequence identity with other GPCRs, most notably the angiotensin II AT1 and AT2 receptors, and the interleukin 8b receptor further indicating that this gene encodes a novel GPCR.

In summary, we have cloned and characterized a human gene encoding a potentially novel hormone receptor. Although the specific nature of the endogenous ligand which binds to GPR15 is currently unknown, future experiments will involve expressing GPR15 and testing different hormones and other ligands for specific binding to this receptor.

Experienced Researcher (Clinical) Category

DISLOCATIONS FOLLOWING TOTAL HIP REVISION WITH ALLOGRAFT. K.P. Panagiotopoulos* and R.D. Masnyk*, P. Ko, Z. Agnidis and A.E. Gross. Division of Orthopaedic Surgery, Mount Sinai Hospital, University of Toronto, Toronto, Canada.

This study evaluated the demographic and surgical variables, as well as risk factors associated with dislocation following total hip revision with allograft.

A retrospective chart review was conducted of 331 patients who had undergone 417 hip revisions with allograft by a single surgeon between 1982 and August, 1995. The variables assessed were: underlying pathology, number of previous hip operations, type of revision prior to dislocation, type of allograft, time to dislocation after revision and the mode of treatment (i.e. closed/open reduction, re-revision or excision arthroplasty).

Forty-three (10.3%) of 417 revisions resulted in 56 total dislocations, forty (71.4%) of which were late dislocations (i.e. at least six weeks post-operatively). Patients having only the acetabular component revised were more prone to dislocation ($p < 0.0001$), as were patients with four or more previous operations ($p < 0.0001$). There were no apparent relationships with respect to underlying pathology, site of allograft or use of a roof reinforcement ring. Forty-two percent of dislocations ultimately required re-revision following unsuccessful closed reduction.

There is a higher incidence of dislocation in patients who have had four or more previous operations. Revising only the acetabular component is also a significant risk factor for dislocation. Therefore, precautionary measures should be taken within these sub-groups of patients.

MD/Ph.D. Student Researcher (Basic or Clinical) Category

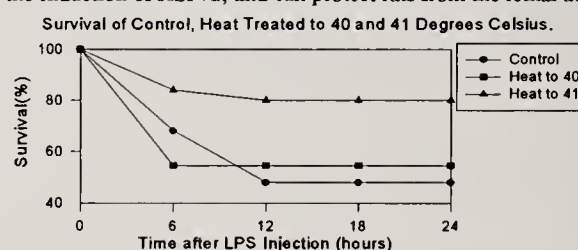
THE PTP1C PROTEIN TYROSINE PHOSPHATASE REGULATES THE CATALYTIC ACTIVITY OF THE PROTO-ONCOGENIC SRC PROTEIN TYROSINE KINASE. A-K. Somani*, §D. Branch and K. A. Siminovich. Dept. of Medicine, Immunology and Molecular and Medical Genetics, University of Toronto and Samuel Lunenfeld Research Institute, Mount Sinai Hospital; §Research Section, Canadian Red Cross Society, Toronto, Ontario Canada.

PTP1C is a SH2 domain-containing cytosolic protein tyrosine phosphatase expressed primarily in haemopoietic cells. Recent data from our group have revealed the association of loss-of-function mutations in the PTP1C gene with expression of the murine motheaten (*me*) syndrome, a phenotype associated with severe lymphocyte dysfunction. Based on preliminary data revealing a role for PTP1C in modulating signalling pathways coupling the T cell antigen receptor to cell proliferation, we examined the potential relevance of PTP1C to regulation of T cell src tyrosine kinase activity. Our data revealed that despite the expression of normal levels of src protein, thymic T cells from *me* mice manifest markedly diminished and essentially negligible levels of src kinase activity relative to the levels detected in wild-type thymic T cells. This finding together with the observation that PTP1C coprecipitates, and thus appears to physically associate with src, suggest that PTP1C induced dephosphorylation of src may be required for expression of src kinase activity. This contention is supported by the observed capacity of recombinant PTP1C to dephosphorylate recombinant src and src immunoprecipitates from normal thymic cells and to restore catalytic activity to src immunoprecipitates derived from *me* thymic cells. Together these data suggest that PTP1C acts to dephosphorylate the kinase inhibitory phosphorylated tyrosine located in the src carboxy terminus and as such plays a critical role in regulating the functional capacity of the src tyrosine kinase in T cells.

Department of Medicine Award

THE EFFECTS OF THE STRESS RESPONSE IN A RAT MODEL OF SEPSIS
E.K. Chu*, S.P. Ribeiro, A.S. Slutsky, Respiriology Laboratory, Faculty of Medicine, University of Toronto.

It has been shown that heating an animal for a brief period of time to a few degrees above its normal body temperature activates the body's stress response which in turn can protect against lethal stimuli. The stress response is characterized by a transient down-regulation of most cellular products and the up-regulation of heat shock proteins (HSP72). Studies of this stress response have focused on its induction *before* the administration of a lethal stimulus. However, the stress response would be of therapeutic value if it were shown to be protective after the occurrence of sepsis. The objective of the present study was to investigate the protective effects associated with the induction of the stress response *after* the intravenous injection of the bacterial endotoxin lipopolysaccharide (LPS). Sixty-one Sprague Dawley rats were injected intravenously with *Escherichia coli* lipopolysaccharide (15mg/kg). They were then randomly divided into three groups and given the following treatment: 1) no treatment (control group), 2) heated to 40°C, 3) heated to 41°C. Western analysis using antibodies directed against HSP72 demonstrated significant expression of HSP72 in the lungs of rats heated to 41°C. Lesser amounts of HSP72 were detected in the lungs of rats heated to 40°C. Survival rates in the rats heated to 41°C, 20/25 (80%), were higher than those of the untreated rats, 12/25 (48%) ($p=0.039$). These findings demonstrate that producing the stress response after LPS injection is associated with the induction of HSP72, and can protect rats from the lethal activity of LPS.



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Bill 26: A Student's Perspective of the *Savings and Restructuring Act*

Michael J. Kalin, M.A. (9T9)

Amidst all the public hearings, debates, and accusations surrounding the government's infamous Bill 26, the *Savings and Restructuring Act*, the desire and eagerness of many medical students to practice medicine in this province has been greatly diminished. For many students, this unfortunate realization does not stem from the fear of future financial constraints or inconvenient placements, but arises from the virulent anti-physician attitude recently propagated by the Harris government. As active participants in socialized medicine, medical students understand the current predicament of the health care system and recognize the desperate need for change. This change requires the efforts of all the parties involved, and will only succeed if it is established as a partnership between the government and health care providers.

“By treating people with the same impudence with which it slashes spending, the government is not only eroding public confidence in the health care system, but coming dangerously close to transgressing individual freedoms and violating inalienable rights.”

It is wrong to assume that Bill 26 is targeted solely against physicians. By continually scrutinizing and investigating physicians, this legislation seriously threatens the quality of care that any patient will receive. Once government acquires the power to intrude on doctor-patient privacy and confidentiality, little remains to be salvaged. The *Savings and Restructuring Act* is a bitter remedy that does not benefit the illness. Its authoritarian approach is medieval in scope and an affront to our valued democratic traditions.

Bill 26 features the largest spending cuts in Ontario's history. The sweeping legislation amends more than forty laws, and is designed to save the province more than three billion dollars in spending. The Bill centralizes decision-making powers at the cabinet level, granting ministers the authority to decide the fates of hospitals and determine the

necessity of services. The Act contains four specific sections which directly affect physicians and health care services. Schedules F, G, H, and I propose extensive changes to existing hospital, drug benefit, and health insurance laws, as well as current agreements between the Ontario Medical Association (OMA) and the government of Ontario.

“...blatant attempts to exclude physicians from the process by demonizing the profession is a personal affront to all responsible physicians...”

Throughout the deliberations on Bill 26, the government has repeatedly vilified the medical profession. This seems to represent a deliberate attempt by the government to portray all physicians as dishonest and reckless members of the health care system. This tactic comes in stark contrast to the government's campaign approach when the Tories personally appealed to individual physicians for election support. Now, a mere seven months after taking office, the government has openly declared its lack of respect towards physicians and its intentions to continue the onslaught by challenging physician eligibility and medical decisions. Frustrated by Minister Wilson's negative approach, Dr. Ian Warrack, President of the OMA has argued that these "errors and misleading impressions present an incorrect record and constitute a personal affront to every doctor in Ontario." Furthermore, Warrack claims that "the Minister has either stated or implied that doctors have been obstructive, irresponsible, fraudulent and unresponsive to the needs of our patients and the health care system." Undoubtedly, physicians and patients are both responsible for some abuse in the health care system. However, by singling out *all* doctors as corrupt, the government has alienated a group which should be, and is prepared to be, their partner in change.

The most contentious issue in this legislation is the requirement placed on physicians to prove the legitimacy of medical treatments. The bill's first draft had granted the General Manager of OHIP the power, after the fact, to solely determine if a service provided by a physician was medically necessary. Due to intensive OMA lobbying, revisions have been made such that the General Manager can

now only refuse to pay after consulting with a "physician." However, the physician under investigation may still be required to repay the costs of services requested by a patient if the Medical Review Committee (MRC) of the College of Physicians and Surgeons of Ontario later decides that the services were not medically necessary. Under Bill 26, the General Manager can publish information pertaining to any physician under review by the MRC. The name, specialty, location, and amount owed by the physician can all be made public.

"If this government is truly committed to the future of medicine in Ontario then it must understand that students can not be treated as pawns in their larger political agenda."

In order to ascertain the necessity of certain services, Bill 26 grants the Minister of Health unprecedented powers to collect, use, and disclose information concerning individual patients. This proposal immediately drew criticism from physicians like Dr. Phil Berger, Chief of the Department of Family Practice at the Wellesley Hospital, who admonished the Minister of Health for "dismissing concerns about patient confidentiality and the privacy of medical records as a 'red herring.'" Even the province's Privacy Commissioner, Tom Wright, expressed grave concerns over the government's intentions, and commented that "privacy, once lost, can never be regained."

Since its fiery introduction, the government has accepted other suggestions from the OMA and the Information and Privacy Commissioner in regard to the confidentiality of patient medical records. A new expedited MRC process has been promised with at least one physician serving on the panel. In addition, new inspectors of the General Manager of OHIP will be removed, and all names and identifying numbers on patient files will be deleted before any publication is made.

While these modifications represent some accommodation on the part of the government, the fact that bureaucrats so freely and thoughtlessly positioned themselves within the doctor-patient relationship remains deeply disturbing. The government has displayed a distressing lack of sensitivity to both the complexity of the issues and the people involved. By treating people with the same impudence with which it slashes spending, the government is not only eroding public confidence in the health care system, but coming dangerously close to transgressing individual freedoms and violating inalienable rights. According to Dr. Beverly Richardson, Chief of Medical Staff Affairs at Women's College Hospital, "Bill 26 basically gives powers to the Minister and/or his designate that are dictatorial, that completely will control the health care system if they are exercised." Dr. Richardson continues, "...I'm a firm believer

that a dictatorship, even a benign dictatorship, even a potentially benign dictatorship is never better than what the democratic process can give us."

Regrettably, Bill 26, even in its final updated form, remains more representative of an authoritarian edict than a democratic doctrine. The legislation still permits the government to eliminate any agreements with the OMA thereby ending any partnership between Queen's Park and the medical profession. In addition, the health minister retains the ability to unilaterally define insured services, control the fee schedule, impose thresholds on earnings, and set "contributions" (read "clawbacks"). As a result, a negative atmosphere has developed as physicians have become more disillusioned with the system. Many physicians share Dr. Ted Rumble's ominous vision that "the Minister is going to completely subjugate the profession. The law no longer protects us, we have signed agreements with the minister which he simply overturns so there's no point anymore to signing a contract."

Bill 26 also grants the Minister of Health the power to issue billing numbers to "eligible" physicians and to determine where doctors can practice. For students, this issue has raised serious concerns. If this government is truly committed to the future of medicine in Ontario then it must understand that students can not be treated as pawns in their larger political agenda. As concerned members of the health care system, students have accepted the responsibility to attend to the needs of those who require care regardless of gender, race, religion, sexual preference, and geographic location. However, as free citizens of this democratic country, students are also entitled to the inherent right to live and practice where they choose without the fear of reprisal or retribution. Stripped of these basic liberties, we risk becoming the subjects of an unwelcomed autocracy.

The *Savings and Restructuring Act* is not a piece of legislation aimed solely at health care reductions. Bill 26 represents the most extreme plan to slash social welfare spending in Ontario's history. Its steep cuts will significantly affect numerous groups including labour, clergy, firefighters, environmentalists, feminists, seniors, teachers, and day-care workers among others. While few would deny the current need for fiscal accountability and restraint, many people are incensed by the government's lack of compassion and unwillingness to negotiate mutually acceptable solutions. In the case of health care reform, the Tories have made the unfortunate decision to unilaterally impose changes. Its blatant attempts to exclude physicians from the process by demonizing the profession is a personal affront to all responsible physicians who have dedicated their lives to the service of others. The manner in which Bill 26 was introduced, debated, and passed should offend all democratically minded individuals. The Harris government obviously needs to be reminded that the privilege to govern is not a mandate to abuse power. Ultimately, this government will learn, like many of its predecessors, that the capacity to rule is given, and can be taken, by the people.

Considering the North

Vincent Lan, B.Sc. (9T9)

When we interviewed for medical school, some of us were asked us if we would work in northern Ontario. Many of us said we would. Some of us meant it, some of us didn't, but we all recognized that there was a distribution problem. Now, graduating doctors face the prospect of being restricted to practicing in underserved areas. We are now being told that we are the ones expected deal with the problem.

“...small centres may offer...more personal contact with the community, an opportunity to perform a greater diversity of medical procedure...and a host of other benefits.”

So, who's going north?

After much posturing, the Government of Ontario and the bodies representing doctors, residents, and medical students, have agreed to disagree. The Ministry of Health will not force anyone to underserved areas at present. They will wait to see where this year's crop of doctors decides to go, but reserve the right to resort to harsher measures in the future. Future measures may involve restriction of billing rights, such that only doctors who go to certain areas will be allowed to bill OHIP. Meanwhile, the Professional Association of Interns and Residents of Ontario (PAIRO), and the Ontario Medical Association (OMA) are speaking out strongly against such a possibility.

Both government and medical bodies are making claims about their right to control medical practice.

The government of Ontario is making the claim that public employees can be publicly distributed. Since there is a physician distribution problem, and since physicians are paid by the tax money of urban and rural Ontarians alike, the government claims the right to control the location of these tax-funded doctors.

Meanwhile, we medical students and residents often make the assertion that other self-employed workers can move freely. Our claim is that a medical practice is a self-managed enterprise similar to any other trade or small business. Since any other tradesman can choose the community in which they wish to practice, we should be able to do the same.

Both claims sound reasonable at first glance, but both claims may ignore some important considerations.

The Ministry of Health would be naive to distribute physicians thoughtlessly, expecting a sudden improvement in rural health care. The practice of medicine does not rest upon the physical presence of a person bearing the degree 'M.D.'. It requires very personal relationships between individual physicians and individual patients. Co-operative and helpful relationships between physicians and their patients can only be discouraged by forced physician distribution, and encouraged if the physician has chosen a community in which to practice.

Meanwhile, one cannot forget that medical care is not directly analogous to a trade or small business. While most trades or small businesses satisfy product-oriented consumer demand, the profession of medicine is concerned with human needs. No one can claim that they have a right to have their consumer demand met. However, any citizen within a system of universal health insurance can make a very strong claim that their legislation-guaranteed human needs should be fulfilled.

Nobody denies these considerations. The government states that they would prefer to avoid coercive measures. Most students recognise a distribution problem that should be addressed. Yet, there remains a gap between the government and the student positions.

“...the idea of an ‘underserved area’ has no reality attached to it.”

What could bridge this gap?

Part of the difficulty is that practicing in an underserved area is not perceived as being a real and attractive option. As medical students, we are taught by urban doctors. All of our clinical education occurs in urban care settings. Thus, all of our professional aspirations are focused upon what is seen in the city. Most medical students come from major centres and only know city life. Having never lived in smaller communities, these are an unknown, and therefore unattractive, entity.

Valid personal concerns have been expressed. Many of us have partners with urban careers, who may not be able to relocate. There are concerns about child-care, schooling, working schedules, and availability of cultural and

religious communities. However, in the absence of information about underserved communities, the worst assumptions are made. It is assumed that partners would not be able to find suitable employment, that there is inadequate child-care, that schooling would be inferior, that working schedules would be horrendous, and that community groups would be lacking.

For some, these factors may constitute good reason not to want to practice in rural Ontario. For others, these concerns may be relieved with more information about underserved communities. Meanwhile, there are many attractive features of smaller communities that are not considered by city-bound medical students. From our sarcastic discussions about 'Northern Ontario', one would think that indoor plumbing and electricity were alien to these distant parts of the world. In reality, smaller centres may offer a safe and peaceful environment, more personal contact with the community, an opportunity to perform a greater diversity of medical procedures, much shorter commutes, nearby outdoors activities, and a host of other benefits.

The key point to note is that while we are well informed about the comparative merits of living in Ontario's cities, and even of the ups and downs of living in Toronto's various neighborhoods, the idea of an 'underserved area' has no reality attached to it. It is a vague, negatively-viewed place that we fear may be imposed upon us. It is not a real option. As long as it is not a real option, very few graduates will locate there, perhaps forcing our government to invoke drastic measures.

In an attempt to dispel the myths of 'Northern Ontario', there may be relatively simple and concrete measures that can be taken during our training. Doctors from underserved areas should speak to us about their practices and lifestyles. Mandatory or strongly encouraged clerkship rotations in underserved areas would allow us to get a better feel for these places.

Once we are choosing an area in which to practice, the Ministry of Health could compile fact sheets comparing various places in Ontario. Place-by-place, these fact sheets could indicate employment opportunities (for partners), schooling availability, library resources, recreational facilities, nearby churches, synagogues, mosques, and temples, average housing prices, grocery prices, entertainment that is available, nearby national parks, nature reserves, lakes, ski centres, and clearly stated professional demands and support services. This may enable us to appreciate the attractions of living in a smaller centre.

Meanwhile, we as students should encourage policy decisions that make practice in underserved areas a real and attractive option. PAIRO has taken a strong lead by lobbying for arrangements that include pay incentives, vacations, professional education leave, and reasonable

working hours. It is important that in addition to voicing our discontent with coercive actions, we propose alternative measures.

Finally, we must seriously consider working in underserved areas. By agreeing to work within and derive personal benefit from this universal health insurance system, we assume a special civic responsibility. If citizens of some parts of this province are not receiving adequate health care, we cannot ignore our obligations to them. While our ultimate decisions of where to practice will be personal, we must seriously consider the option of working in smaller communities or else be negligent in our duties.

“As long as it is not a real option, very few graduates will locate there, perhaps forcing our government to invoke drastic measures”

At this juncture, the way in which the government and student/resident bodies interact will color many events of the future. Resource allocation is today's hot medical issue. Physician allocation, as a policy dilemma, is an early and very personally-felt expression of this trend. If relations between government and young physicians are combative, the government will attempt to consolidate its administrative power while physicians protest strongly. The government has already moved to negate the OMA's right to negotiate for doctors. A lack of communication between care payers and care providers can only hurt patients. If, on the other hand, government and young doctors can work together to resolve the problem of physician distribution, this would be a good start as we begin to confront difficult issues of resource allocation.

We may or may not have been sincere when, during our interviews, we said we'd go north. However, we were sincere when we said we wanted to be doctors. By becoming physicians in Canada, we inherit an obligation to the public good. If public medical needs exist, we cannot escape our duty to fulfill these needs. The government must remember, however, that we didn't say we wanted to be civil servants. In undertaking the study of medicine, we chose to work with people, and we want to choose the communities that we'll be a part of.

The government and young doctors must work together, to ensure our freedom of choice and yet find a way to meet our obligations through these choices.

Delivering Good Health Care to Underserviced Areas

Michelle Wise, B.Sc. (9T8)

In my capacity as Vice President External to the Medical Society at the University of Toronto, I represent medical students to the Ontario Medical Association (OMA) and the Professional Organization of Residents and Interns of Ontario (PAIRO). Through my position, I have come to appreciate that reaching the goal of practicing as a physician is intricately bound to the politics of the day.

This has been particularly evident of late, as on January 29th, in the face of much public opposition, the Conservative government passed Bill 26, *The Savings and Restructuring Act*. This Bill effectively eliminates the collective bargaining rights of the OMA, thus eliminating any partnership that previously existed between the medical profession and the Ministry of Health. Although the Bill covers a plethora of health and non-health related issues, the one on which I will focus is one that affects medical students most directly.

Bill 26 permits the Minister of Health to make decisions unilaterally about health care, and use this power it to tell all newly graduating doctors where they may practice. There are about 70 communities across Ontario that are designated by the government as medically "underserviced areas." Under the new legislation, new doctors can be told that unless they elect to practice outside of an "overserviced area", they will be ineligible to receive a billing number, thus rendering them unable to practice medicine in Ontario. This measure empowers the government to forcibly uproot new doctors from their families, friends, and cultural and religious affiliations, and install them in a community that is totally alien to them. Not only is this impractical, but unfair.

Moreover, as opposed to being a temporary measure for a prescribed period of time, such as the first year in practice or several weeks a year, this will be a *permanent* arrangement. Clearly this measure has gone too far in intervening in the lives of doctors.

It is also distressing that the decision to proceed with these billing number restrictions was made without input from those whom it will affect most, namely medical students, residents and interns. It was made without exploration of the alternative solutions that have been proposed, and without implementation of the recommendations made in recent reports.^{1,2} Decisions that will impact so dramatically on the lives of future doctors should be discussed, and not imposed.

There is broad agreement among the medical community and the government that a problem exists. Current recruitment efforts have not been successful in attracting enough doctors to establish practices in many communities across Ontario. The challenge is to find a solution that will work, both for the health care providers, and more importantly, for the communities themselves, so that quality of care is not compromised.

“Current recruitment efforts are not succeeding in attracting enough doctors to establish practices in many communities across Ontario. The challenge is to find a solution that will work, both for the health care providers and for the communities...”

Coercive and forceful measures will not solve the problem. Patients will be done a disservice if they are cared for by doctors who are neither interested nor motivated to be a part of the community. The current model of medical education focuses on the importance of the doctor-patient relationship. How can a positive relationship evolve if one has been forcibly installed into it? The atmosphere created by the passage of Bill 26 has put doctors and government into an adversarial relationship instead of one of partnership, and this is detrimental to the quality of health care.

The use of legislative power to achieve the Ministry's goal may actually backfire, and *reduce* the number of doctors who end up practicing in areas that need them the most. When faced with the ultimatum of practicing in an "underserviced" area or not receiving a billing number, many graduates will elect to leave Ontario to practice elsewhere, rather than have their rights infringed upon.

The government does not have to wait to wait to see the consequences of their actions. A recent University of Toronto study of residents in the Department of Family Medicine found that around 80% of them are planning to seek practice in the U.S. when they graduate.³ Compare this to a previous survey from before the introduction of Bill 26 which found that 35% of the graduating class, an alarming number in its own right, intend-

ed to go to the U.S.⁴ This mass exodus represents a serious threat to the provision of services in Ontario.

Worse, these restrictions may change the minds of those who *do* intend to establish their practice in rural or small communities. Such individuals may fear being locked-in to their decision by being denied the possibility of returning to a larger centre.

The issue for many is one of personal and professional freedom. The dictatorial and hostile environment created by the government alienates the very doctors who should be encouraged to stay.

Most importantly, imposing billing number restrictions is not a long-term solution. It will get some doctors where they are needed immediately, thus "solving" the problem in the short-term, however, it fails to address concerns that medical residents have about working in small communities for the rest of their lives. Many residents are worried about practicing in isolation, with only limited support from specialists, and without the benefit of team consultation. Another concern is the stress of being on call 24 hours a day, 7 days a week.

Thus, if doctors do not want to be in these communities in the first place, and nothing is done to improve the working conditions that lead to burnout, they will be quick to flock back to Toronto, London, and Kingston, at the first opportunity. So much for the continuity of care.

PAIRO has found that many of their members *want* to work in underserved areas, probably in numbers sufficient to fill the gaps over the next few years. In consultation with Northern Ontario communities, they are developing a comprehensive recruitment and retention program which will keep doctors in the North. This plan should also be more effective because it deals directly with the key issue of physician burn-out.

A survey conducted by the Medical Society at University of Toronto in November 1995 found that three quarters of second year medical students would be enticed to work in "underserved" areas by non-monetary incentives. These included guaranteed coverage by replacement doctors (locums), time for occasional and much needed breaks, easier access to Continuing Medical Education, and reasonable schedules for on-call and emergency room coverage. A flexible incentive-based approach is the only practical solution.

Instead of bulldozing ahead with a strategy for which there is no supporting evidence, the government should work on implementing the recommendations made in recent reports on this issue.^{1,2} For example, changes to medical education that increase the amount of exposure to rural and small communities at the undergraduate

level may draw more medical students to them in the first place. As well, a stronger orientation to the urgent professional and physician needs of rural medicine is recommended.

To summarize, the strategy of imposing billing number restrictions works neither for the communities nor for the residents and interns. It does not address patient issues such as continuity and quality of care, nor does it address provider issues such as improving their working conditions in small and rural communities. Without a comprehensive recruitment and retention effort, no amount of misguided legislation or restrictions will solve Ontario's health care problem.

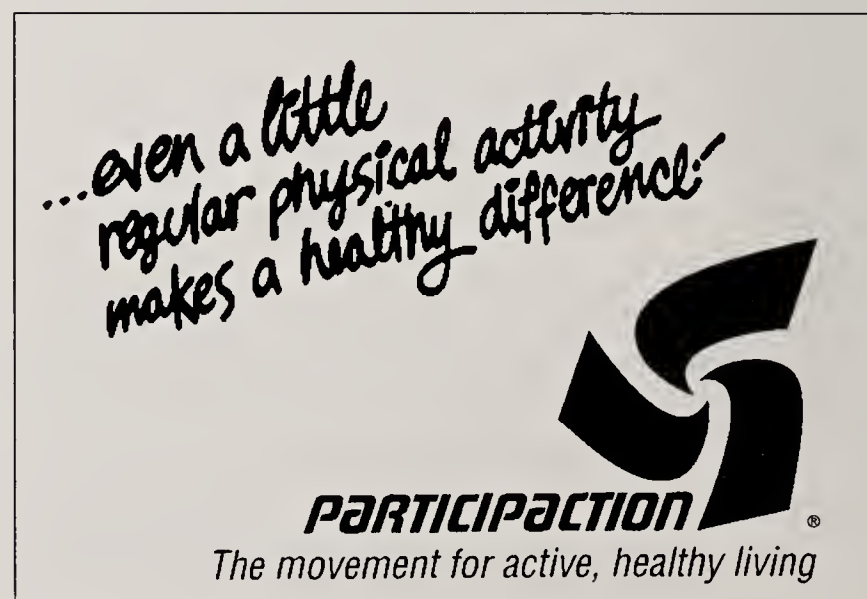
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Bioartificial Pancreas

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Insulin-dependent diabetes mellitus (IDDM) is a disease precipitated by autoimmune destruction of the insulin producing β cells of the pancreatic islets of Langerhans. The most common form of therapy for this disorder, injection of purified insulin, has remained almost unchanged since the discovery of the hormone in 1922 by Banting and Best. Although the administration of insulin by injection is clearly a life-saving intervention for patients devoid of β cells, this approach falls short of the remarkable titration of insulin delivery and consequent control of glucose levels achieved in normal individuals. This control is brought about by the capacity of the normal cell to respond to moment-to-moment changes in the plasma glucose concentrations over the physiological range. In the absence of such physiological control of the plasma glucose concentrations, the daily injection of insulin has not been able to prevent the common complications of the disease, namely nephropathy, retinopathy, neuropathy as well as vascular complications. This has been confirmed in the recent Diabetes Control and Complications Trial (DCCT) which has demonstrated that intensive treatment of patients with IDDM with tight glycemic control close to the normal range effectively delays the onset, and slows the progression, of the various diabetic complications. Therefore, it becomes mandatory to develop methods, applicable early in the course of the disease, and in any type 1 diabetic patient, for obtaining perfect metabolic control without increasing the risk of severe hypoglycemia. Consequently, the transplantation of islet tissue, either as whole pancreas or as isolated islets has been pursued because these techniques can provide near-normal blood glucose control and thus have the potential to prevent diabetic complications.

With the emergence of effective immunosuppressive agents and improved surgical techniques, the number of whole or segmental pancreas transplantations has steadily increased with much improved patient and graft survival. By November 30, 1995, 7,505 pancreas transplants were reported to the International Pancreas Transplant Registry. However, the whole pancreas trans-

plantation represents a formidable surgical procedure. In addition, the necessity for life-long immunosuppressive therapy has been associated with significant morbidity and mortality as a result of opportunistic infection and spontaneous neoplasms, as well as drug-induced toxicity and metabolic complications.

In view of the many problems associated with the whole pancreas transplantation, grafts of isolated pancreatic islets represent the most promising approach to the restoration of the pancreas' endocrine function in patients with IDDM. Unfortunately however, human islet transplantation has so far been performed only with limited success. As of June 1993, the total number of cases (since the beginning of human clinical transplantations) reported to be off insulin for one month or longer was 23. The need for long-term immunosuppression and the acute shortage of organ donors represent the most pressing obstacles to human islet transplantation. Consequently, it becomes obvious that if the goal of islet transplantation is to succeed, it is necessary to develop methods that will enable the transplant of non-human islet cells in the absence of immunosuppression.

In order to overcome the immunorejection problem and the need for immunosuppression, and to circumvent the potential for disease recurrence, the concept of immunoisolation has been advanced. This is achieved by enclosing the pancreatic islets by semipermeable and biocompatible membrane (bioartificial pancreas). Low-molecular substances, such as nutrients, electrolytes, oxygen, and hormones are exchanged across the membrane, while immunocytes and immunoglobulins are excluded. This approach has the potential not only to allow allogenic transplantation without immunosuppression, but also to allow the use of xenografts.

In the form of a vascular implant, the islets can be distributed in a chamber surrounding the membrane, and the device is implanted as a shunt in the vascular system. The limitations of the vascularized devices are all associated with the creation of an arterio-venous shunt, i.e. requirement of major surgery, possible vascular throm-

basis, and a potential for cardiac stress caused by a significant volume of shunted blood. Most importantly, an accidental breakage of such a unit may result in a serious haemorrhage.

Alternatively, the islets can be immunoisolated within diffusion chambers and placed intraperitoneally, subcutaneously or in other sites. Numerous devices of this type have been evaluated during the last several decades. These include disk-shaped diffusion chambers, Millipore cellulosic membranes, hollow fibre diffusion chambers and wider-bore tubular membrane chambers. Membrane materials used to fabricate these devices include polyvinylchloride, polyamides (nylon), polypropylene, polycarbonate, cellular nitrate and cellulose triacetate.

The method of islet transplantation using the above mentioned devices is frequently referred to as macroencapsulation. The common feature of this approach is that a great number of islets are placed within the chamber of the device. This severely affects the diffusion dynamics of the system. Consequently, the problem of cell death or dysfunction as a result of oxygen supply limitations, or accumulation of wastes or other agents is likely to be severe. Chambers retrieved several weeks after implantation often contain a central necrotic core. Another problem is the frequent breakage of the diffusion chambers which can cause not only loss of islet function but also intraperitoneal inflammatory responses. The problems posed by the large volume of the implanted devices as well as a possible fibrosis of the chamber surfaces can further aggravate the situation. Typically, the use of these devices can result only in a short term amelioration of diabetic hyperglycemia.

In another approach to immunoisolation we invented semipermeable, alginate-polylysine-alginate (APA) biocompatible capsules to enclose individual islets (microencapsulation). Since our original invention in 1980 many applications of the microencapsulation concept have been developed with many centres now studying cell encapsulation. We have considerably improved the capsule construction since its conception 16 years ago. In addition to altering the chemical composition of the membrane, we have significantly reduced the size of the capsules. This has not only improved the diffusion dynamics and reduced the over all volume of the implant, but has added significant strength to the capsule. It has been demonstrated that by virtue of improved sphericity, surface smoothness, and most importantly, increased strength, the smaller size of the microcapsules has an important bearing on the lifespan of the graft.

In our earlier experiments using rodents as both donors and recipients we demonstrated that both allografts and xenografts of microencapsulated pancreatic islets were protected from immunorejection and that in both streptozotocin-induced and spontaneously diabetic mouse and rat recipients, diabetes could be reversed for the lifespan of the animals.

Recently, in an unprecedented pre-clinical study we have demonstrated that intraperitoneal xenografts of microencapsulated porcine islets into naturally diabetic non-human primates result in normalization of diabetic hyperglycemia for up to 27 months without recourse to exogenous insulin or to immunosuppression. This is the first report ever on long-term discordant xenograft function resulting in a physiological glycemic control without recourse to immunosuppression in a large animal model. The results of this truly "world-first" study warrant a clinical trial in human diabetics. If successful, our microencapsulation/transplantation concept may soon eliminate diabetes as a major health risk.

Dr. Anthony Sun is a professor at the University of Toronto in the Department of Physiology. His main research interests are in the development of bioartificial organs including pancreas, liver, parathyroid and pituitary.

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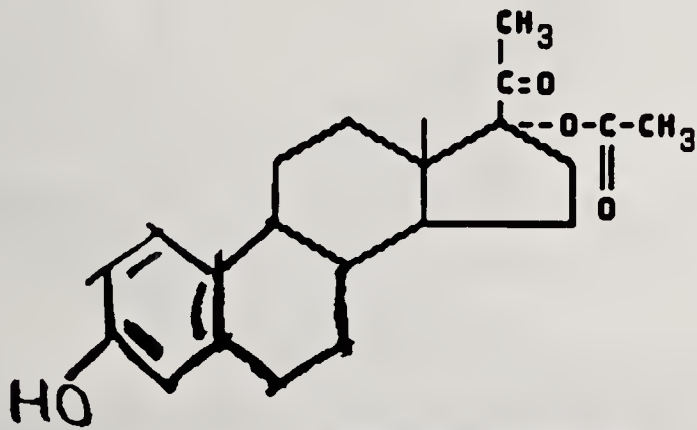
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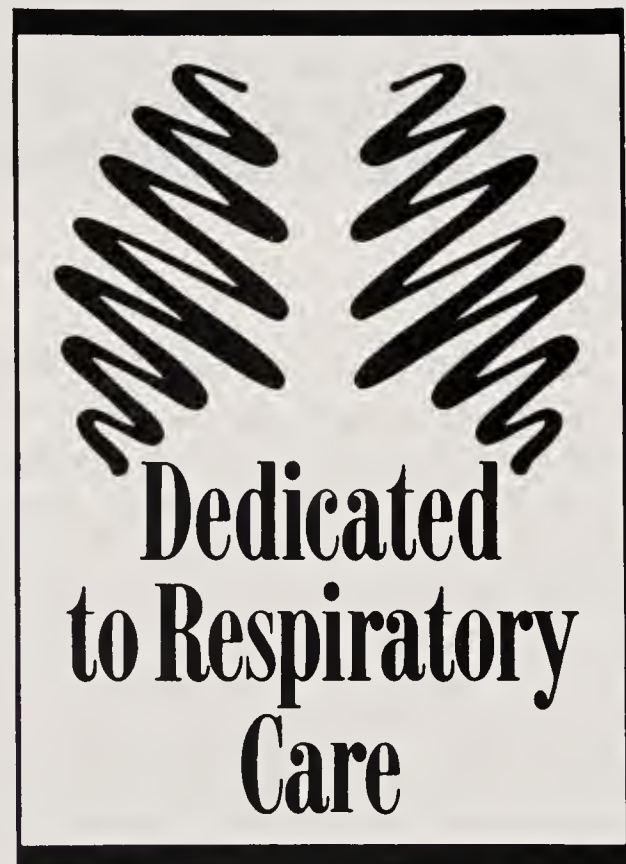
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Benign Paroxysmal Positional Vertigo: A Review

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DINO PULERÀ

Abstract

Benign paroxysmal positional vertigo (BPPV) is probably the most common cause for acute episodic vertigo. It is generally a self limiting condition, but in some, it can be quite disabling. In this report, we provide a general overview of BPPV with an emphasis on describing the essential aspects of the history and physical examination as the basis upon which the diagnosis is made. The pathognomonic features of BPPV are highlighted to further aid the reader in establishing a diagnosis. Treatment options for those with incapacitating symptoms are also explored. The intent of this article is to give the reader both a fundamental appreciation as well as a general approach to this relatively common condition.

Introduction

Vertigo is described as a hallucination of movement involving oneself or one's environment. Typically

described as a "spinning or circling sensation", its presence is usually reflective of a disturbance involving the vestibular system.¹ Benign paroxysmal positional vertigo (BPPV) is a particularly common but specific type of vertigo which occurs with changes in head position; especially those involving recumbency of the head to either the left or right. Although BPPV may occur following traumatic head injury, viral infection, or ear surgery, in many cases, no causative factor can be identified.

Schuknecht (1969) postulated "cupulolithiasis" as the pathogenesis of BPPV and demonstrated granular basophilic deposits in the posterior semicircular canals from patients with premorbid symptoms consistent with BPPV.² The origin of these deposits is presumably from the detachment of mineral crystals from hair cells of the utricular otolith organ (Figure 1). However, as of yet, this has not been completely ascertained.

Patients commonly present with acute attacks of transient vertigo (seconds to minutes) which are precipitated



Figure 1: BPPV Cupulolithiasis. Cross section through temporal bone and semicircular canal demonstrating cupulolithiasis (stained H & E).

by certain head positions. The vertigo of BPPV is associated with a distinct pattern of nystagmus (defined as involuntary rhythmic movements of the eyes) which is *not* accompanied during a provocative maneuver by hearing loss or tinnitus (unwanted head noise).

The diagnosis of BPPV is largely a clinical one and also one of exclusion. The natural course of BPPV is self-limiting in most cases and usually spontaneously subsides in a period of weeks to months. However, in a very small subset of patients, symptoms may recur after months or years, and may even fail to resolve and become quite incapacitating.² For these patients, treatment options include physical therapy techniques as well as surgery.

History

The importance of history in evaluating the dizzy patient cannot be overemphasized. Indeed, well over 90% of diagnoses are made by history alone.³

Initially, the patient will present to the physician's office with a chief complaint of 'dizziness'. To the patient, the term dizziness will be used to describe their subjective sensation of altered sense of well being which may result from a wide variety of conditions. These may include: 1. *psychogenic causes* such as stress, anxiety or panic attacks, 2. *orthostatic hypotension* secondary to underlying cardiovascular pathology or medications such as antihypertensives, antiarrhythmics, or tranquilizers, and of course, 3. *true vertigo* which may arise from either inner ear dysfunction (peripheral vestibular) or from defects in the central vestibular pathways of the brainstem (central vestibular).¹

Once it has been established that the dizziness the patient experiences is actually vertigo as opposed to "lightheadedness" or "fainting spells", it is important to

differentiate between peripheral and central dysfunction. The presence of focal neurologic dysfunction (dysphagia, dysarthria, paresis, parasthesia, incontinence of bowel or bladder activity, etc.) requires further investigation to exclude a central lesion as the cause.¹

All patients should be asked whether they have suffered a recent head injury, if they have had a recent viral illness (i.e. upper respiratory tract infection), or if they have had any prior ear infection or surgery. In addition, it should also be ascertained whether or not there is any associated otalgia, tinnitus, hearing fluctuation or loss, or aural fullness. The timing and duration of the vertiginous episodes must also be clarified in order to further narrow down the differential diagnosis (Table 1).

Perhaps the two most important and revealing questions to ask the patient are: 1. "What happens when you lie back in bed in the evening or roll over?" and 2. "What happens if you stoop down and rise or turn your head too quickly?". Patients with BPPV may describe, often without prompting, objective spinning of their surroundings whenever they happen to partake in the aforementioned activities.⁴ Vertigo and nystagmus become intense within a few seconds of assumption of the provocative position, but last briefly (seconds to minutes).⁵ There is often an associated feeling of nausea and sometimes vomiting. Patients will often complain of being awakened frequently during their sleep due to severe dizzy spells which occur when they inadvertently roll over in bed. Not surprisingly, many patients will admit to being apprehensive about standing up on waking in the morning as they fear they may lose their balance.

Examination

As with any patient presenting with vertigo and dizziness, the clinician should always perform a thorough physical examination to exclude some other underlying process as a cause of the patient's symptoms. This should include: vitals with emphasis on orthostatic changes, otological examination, cranial nerve examination, cardiovascular examination, a full neurological assessment with emphasis on any cerebellar findings, and an attempt to reproduce symptoms through hyperventilation.

Next, the Dix-Hallpike (or Barany-Nylen) maneuver should be performed (Figure 2). Ideally, this test should be performed with Frenzel's glasses which are basically magnifying lenses that allow the clinician to better assess the patients' eye movements during the maneuver. In addition, they suppress ocular fixation on the part of the patient which may inhibit the nystagmus.



Figure 2: The Dix-Hallpike (Barany-Nylen) Maneuver. If nystagmus characteristic of BPPV is demonstrated, the diagnosis is virtually clinched.

The Dix-Hallpike maneuver is performed by placing the patient in the supine position with their head extended to approximately 30 degrees, and turned to one side (right or left). This position should be held for approximately 15-30 seconds and any eye movements present during this time should be carefully observed. The patient is then brought back to the upright sitting position. The maneuver is then repeated to the contralateral side. Often during the maneuver, the patient will become distressed complaining that they feel a 'dizzy' attack coming on and may even object to being repositioned.

The nystagmus of BPPV has several unique and distinguishing characteristics which are pathognomonic. These are:

1. *Rotatory nystagmus:* The eye rotates (so-called geotropic rotatory nystagmus) about an axis extending from the cornea to the retina with the quick beat directed towards the pathological ear typically between 5-30 seconds. When brought upright there is a reversal of the nystagmus (so-called ageotropic rotatory nystagmus) typically of shorter duration.
2. *Latency:* Upon assuming the new head position, an interval of several seconds will pass before the nystagmus actually begins.
3. *Fatigability:* Without changing the head position, the nystagmus will gradually subside usually in approximately 10 seconds and eventually stop.

4. *Reproducible symptoms:* The patient experiences subjective vertigo, nausea, and distress while the nystagmus is active.⁴

If the Dix-Hallpike maneuver is performed correctly and reproduces the aforementioned results, the diagnosis of BPPV is virtually clinched.

Investigations

The key to diagnosing BPPV lies in taking a thorough history and performing a sound otoneurological exam. If the diagnosis of BPPV is made clinically, further investigations are, in general, not helpful. However, if there is still some doubt as to the correct diagnosis, further investigations should be ordered as indicated.

If the symptoms are thought to be due to peripheral causes, test of end-organ function are usually indicated. These include both conventional and evoked-response audiometry and electronystagmography (ENG).¹

When there is a concern that a CNS lesion may be present, then computerized tomography (CT) or magnetic resonance imaging (MRI) should be requested. An electroencephalogram (EEG) may be ordered if there is a concern that an epileptic focus is present. Other investigations, such as a lumbar puncture, angiogram, radionuclide or brain scan should only be ordered if the patient's symptoms warrant these specific investigations.¹

Management

Given that the condition of BPPV is usually self limited and will spontaneously resolve within weeks to months, expectant management is indicated. In these cases, the patient should be informed of the natural course and advised to try to avoid the positions which cause them to experience symptoms until resolution eventually occurs. Drug therapy is generally ineffective, though a short course of a benzodiazepine such as ativan, or diazepam may be helpful for the anxious patient.⁴ Patients should also be aware that even after their symptoms completely abate, there is still a possibility for recurrence in the future. In this case, they should be told not to hesitate in making arrangements for follow up so that other pathology may be carefully excluded.

Uncommonly, symptoms in a small subset of patients may persist for several months or years. In rare cases, the patient's disability from this is so great that more specific therapy is required.⁴ Initially, these patients may be offered conservative treatment through the particle repositioning maneuver. This therapy involves a series of head movements which theoretically displaces the offending particles from the posterior canal through the

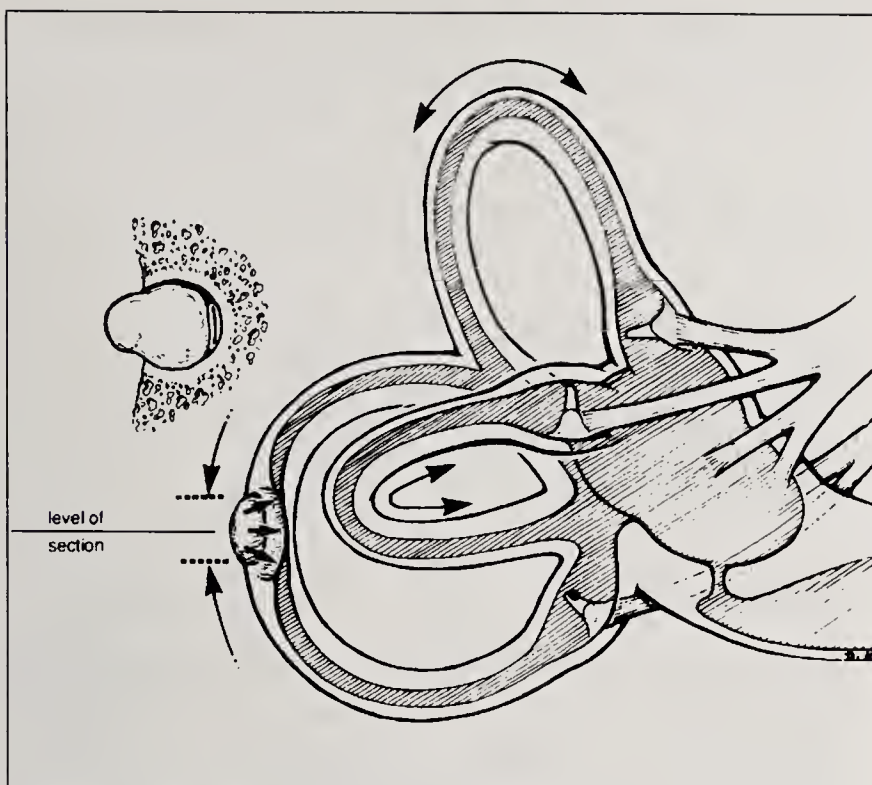


Figure 3: Schematic basis for posterior canal occlusion surgery. Prevents circulation of endolymph thereby physiologically preventing deflection of the cupula and BPPV.

common crus into the vestibule where they no longer induce pathological responses.⁵ It is a simple bedside technique which takes approximately 30 minutes to perform and has been found to be 80%⁵ effective in curing or significantly improving symptoms.

Failing conservative therapy, patients may then be offered surgical treatment. Surgical options include: labyrinthectomy, singular neurectomy, and posterior semicircular canal occlusion.

Labyrinthectomy is very effective in relieving the symptoms associated with BPPV, but inevitably causes sensorineural deafness. It is now reserved for those patients who have no useful hearing in the affected ear.²

Singular neurectomy deafferents the posterior canal ampulla and is also very effective in relieving the signs and symptoms of BPPV.² Although it has been the recent mainstay of surgical treatment of BPPV, it is also one of the most difficult procedures to perform in otology.² Gacek (1982) reported results of 97 procedures performed by 10 surgeons in which 91% of the patients were relieved of BPPV.⁷ Singular neurectomy, in the best of hands has a 7.3% incidence of sensorineural hearing loss and an 8.3% failure rate.² To date, there are only a few surgeons still doing the procedure.⁷

Posterior semicircular canal occlusion is a relatively new operation used in the treatment of BPPV (Figure 3). Although the numbers are small, excellent results have thus far been reported.⁸ The operation is technically less difficult than singular neurectomy and complications have been minor.² Experience so far indicates that posterior semicircular canal occlusion is a safe and effective

alternative to singular neurectomy in the treatment of intractable, incapacitating BPPV.²

Summary

Benign paroxysmal positional vertigo is probably the most common cause of episodic vertigo. The diagnosis of BPPV is made by taking a thorough history and performing a focused physical examination which should include the Dix-Hallpike (Barany-Nylen) maneuver. In most cases, BPPV is self-limited and symptoms should resolve in weeks to months. However, in a few patients, BPPV can be intractable and incapacitating. For these patients, treatment options are available and include physical therapy techniques and/or surgery.

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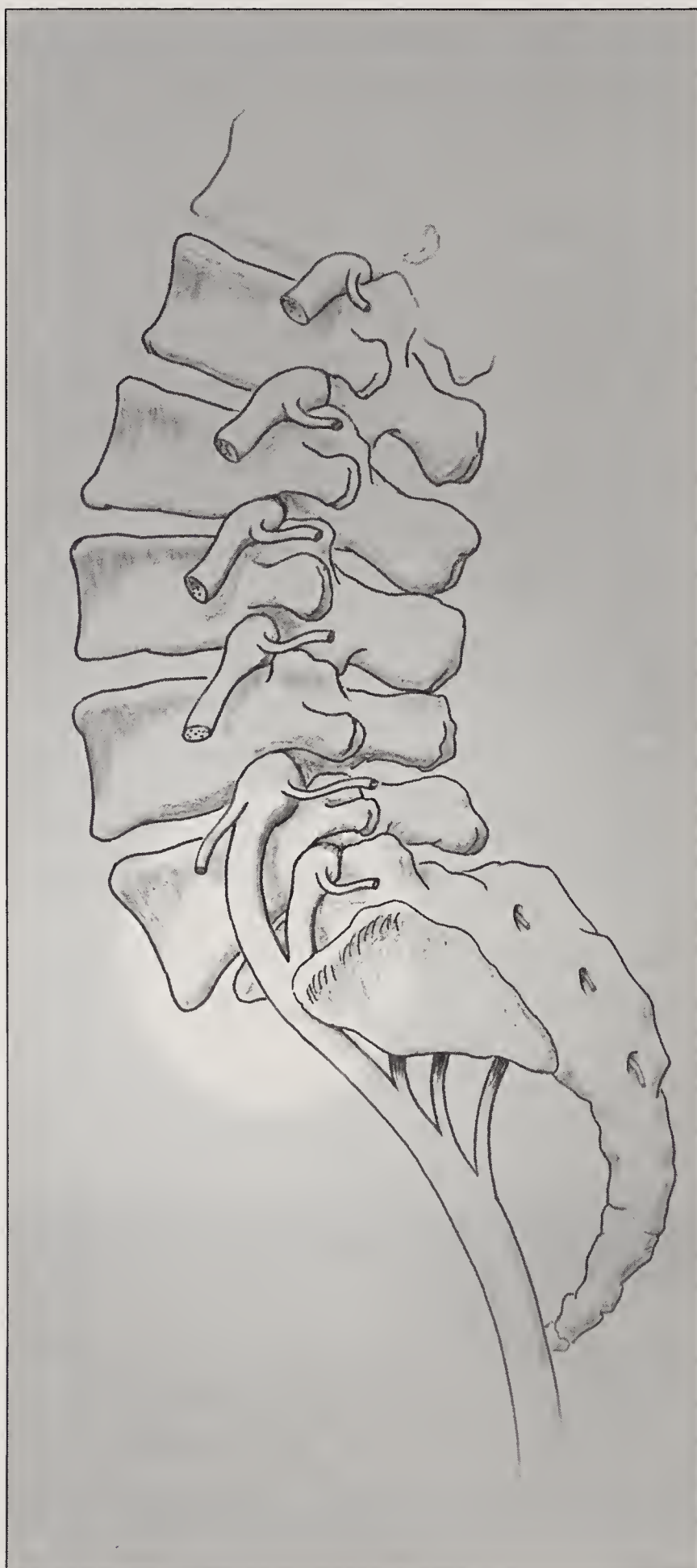
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Spondylolisthesis

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Abstract

Spondylolisthesis is a disorder involving the forward displacement, or slip, of one vertebrae on another. Spondylolisthesis is one of the most common causes of back pain and sciatica in children and adolescents. Nonetheless, a great deal of emphasis is presently being placed on the presentation, evaluation, and treatment of this clinical entity as it presents in adulthood. Recent advances in spinal surgery have led to a tremendous amount of interest in the possible surgical management of this condition in adults.

This paper describes the general classification of spondylolisthesis, but focuses on the etiology, natural history, presentation and treatment of the types of this condition presenting in adulthood. It is without question that the proper management of this condition in the adult population requires a thorough understanding of the etiology and natural history of spondylolisthesis.

Introduction

Herbinaux, a Belgian obstetrician in the 1700's, was most likely the first person to describe spondylolisthesis¹. Kilmen, in 1854, subsequently described the term spondylolisthesis which is derived from the Greek words "spondylos" (meaning vertebrae) and "olisthesis" (meaning to slip). It was not until nearly 1900, however, that Franz Ludwig Neugebauer first brought spondylolisthesis to the clinical attention of the medical community by classifying the types of this condition with respect to etiology and pathogenesis¹. Since then, spondylolisthesis has been recognized as a distinct group of disorders involving the forward displacement of one vertebra on another.

Classification

The classification of spondylolisthesis most widely accepted today is based on the concepts developed by

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Wiltse, Macnab, and Newman in 1976². They described and illustrated the following five basic types of spondylolisthesis (Figure 1).

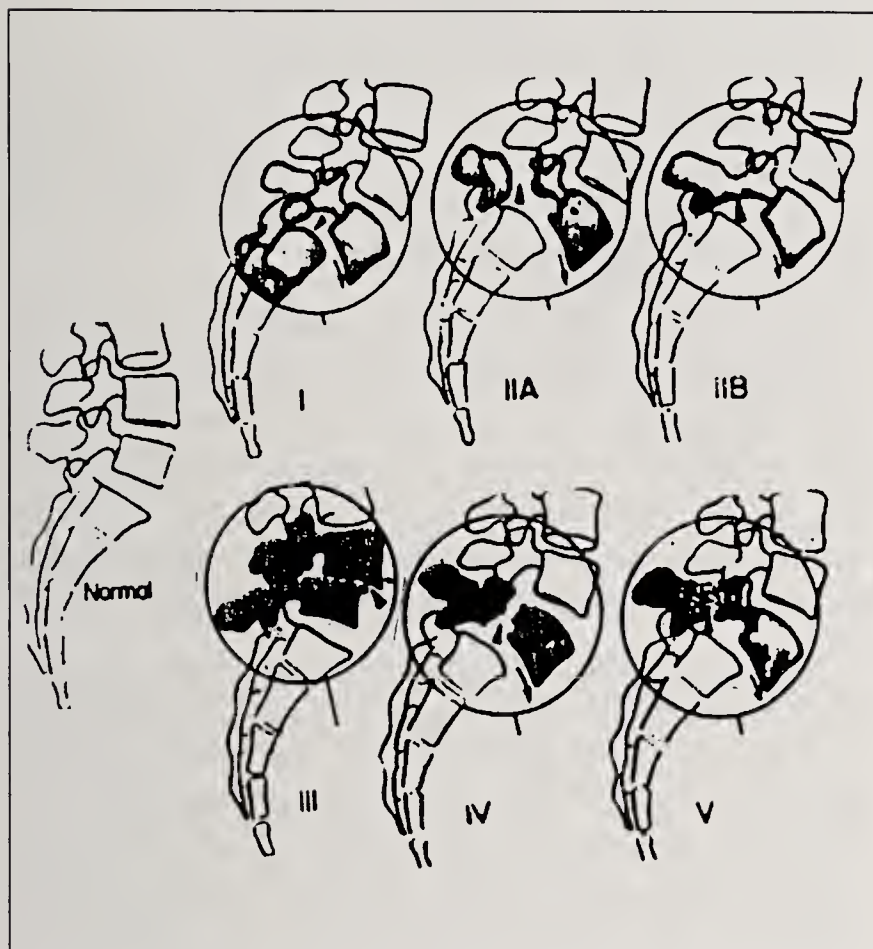


Figure 1: The classification system for spondylolisthesis. (Adopted with permission from reference #5)

TYPE I CONGENITAL OR DYSPLASTIC SPONDYLOLISTHESIS

There is a very strong hereditary component to this type of spondylolisthesis. This subtype is characterized by dysplasia of the upper sacrum and, more importantly, the facet joints. Wiltse and Rothman³ deduced that this dysplasia affected the ability of the lumbar spine to resist shear forces resulting in the forward displacement of the fifth lumbar vertebrae on the sacrum. This form of spondylolisthesis usually starts in childhood and may present in a listhitic crisis characterized by severe back pain, hamstring spasm and possible neurological compromise.

SUBTYPE A Axially oriented dysplastic articular processes.

SUBTYPE B Sagittally oriented dysplastic articular processes.

TYPE II ISTHMIC SPONDYLOLISTHESIS

The basic lesion in this type of spondylolisthesis is in the pars interarticularis – the connecting link between the pedicle, transverse process, lamina, and the two articular facets acting as the pivotal centre. There is also a con-

genital predisposition in this group. The lesion in the pars consists of a stress or fatigue fracture. Both subtypes in this group are probably a different manifestation of the same disease process.

SUBTYPE A Lytic – fatigue fracture of the pars.

SUBTYPE B Elongated but intact pars.

TYPE III DEGENERATIVE SPONDYLOLISTHESIS

Wiltse⁴ believed that this type of spondylolisthesis results from long-standing intersegmental instability and involves remodelling of the articular processes at the level of the slip. This type rarely presents before the age of forty.

TYPE IV TRAUMATIC SPONDYLOLISTHESIS

Wiltse⁴ emphasized that this type was the result of major trauma to the supporting bones of the spine other than the pars. The forward displacement in this type occurs gradually and is not the result of a fracture dislocation.

Type V Pathological Spondylolisthesis

This lesion is the result of generalized or local bone disease. Any portion of the supporting structures may be affected. This lesion is of little importance but it is mentioned in this article for the sake of completeness.

Wiltse and Rothman³ then added Type VI, Post-Surgical Spondylolisthesis. The most common etiological factor in this group is extensive surgical decompression. There is a congenital etiology of both the dysplastic and the isthmic types of spondylolisthesis³. The major types of this condition which most commonly present in adulthood are isthmic and degenerative spondylolisthesis, which will form the focus of the remainder of this article.

Investigations

Plain x-rays provide the most essential information required in the investigation of spondylolisthesis. Anteroposterior and lateral views should be taken and should include both the lumbosacral and thoracolumbar junctions⁵. The Ferguson oblique views are best at demonstrating the pars interarticularis and should be obtained if any doubt exists about the existence of a pars defect⁵. In addition, the Ferguson views are effective in detecting a unilateral pars defect which accounts for 20% of pars defects⁶. Supine flexion-extension views are often used in evaluating translational mobility. Tomograms may also help outline the bony contours

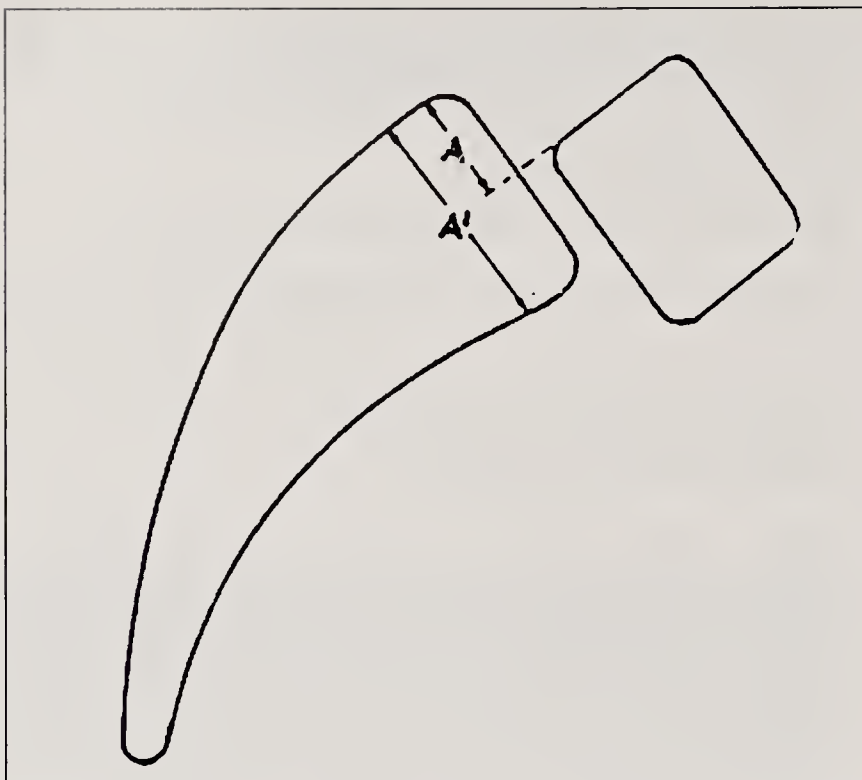


Figure 2: The extent of anterior displacement as modified by Taillard. The extent of displacement is determined by: $A/A' \times 100$.

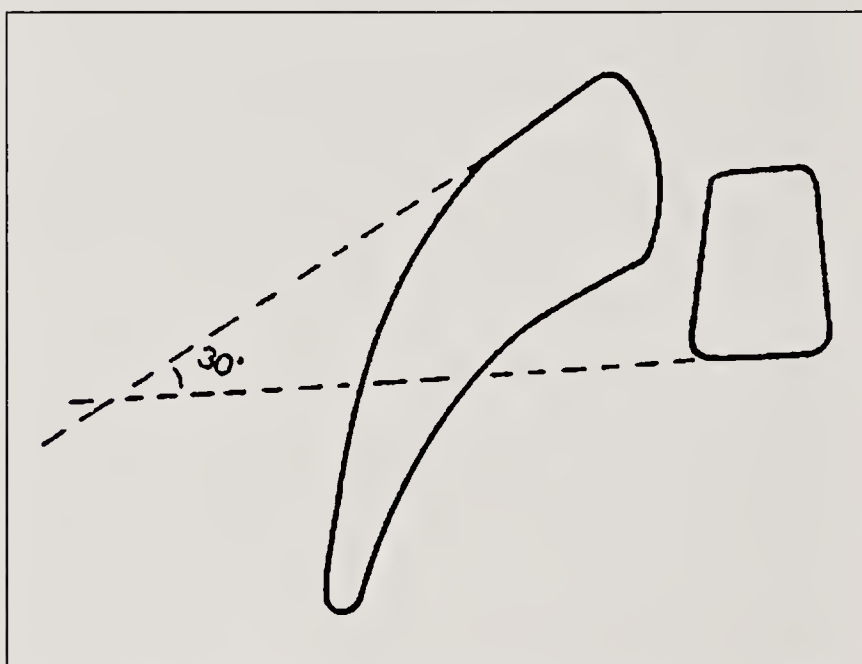


Figure 3: The calculation of the sagittal rotation show schematically.

(Figures 2 and 3 adopted with permission from reference #7)

and may be of assistance if accurate measurements are needed.

Measurements of the various aspects of the deformity associated with spondylolisthesis have received much attention in the medical literature because of the increasing interest in surgical correction. Although a discussion of all the terminology and measurements are beyond the scope of this article, the following two important measurements will be discussed: anterior displacement and sagittal rotation.

Two principle methods in determining the degree of anterior displacement have been used. The first is the Meyerding method. Meyerding divided the anteroposterior diameter of the superior lumbar vertebrae into quarters and assigned a grade of I, II, III, and IV to slips of 25%, 50%, 75%, and 100% respectively. The second method was described by Taillard and is the technique preferred today because it is more precise⁷. Taillard expressed the forward displacement of the superior segment as a *percentage* of the anteroposterior diameter of the inferior segment (Figure 2).

Sagittal rotation describes the rotational or angular relationship between the fifth lumbar vertebrae and the first sacral vertebrae. It has also been described as "sagittal roll", "sagittal rotation", or "slip angle". Boxall⁸ defined this as the angle formed by the intersection of a line drawn along the posterior aspect of S1 and of a line drawn along the anterior border of L5 (Figure 3).

Very few patients require any additional imaging studies, but a number of different tests may be used in selected patients. Radionuclide scintigraphy (^{99}Tc) has some limited use in the evaluation of spondylolisthesis. It is very sensitive in detecting early stress fractures and, thus, may be a useful test in young athletes and children, but a positive scan is found in only about 15% of patients with chronic pain^{9,10}. Bone scans may be abnormal in patients with a unilateral pars defect and may be useful in athletes in order to evaluate healing and judge their return to a high level of activity¹¹. CT scans, although very sensitive in the diagnosis of a pars defect, is best utilized in the adult population in the evaluation of other possible causes of radiculopathy. MRI can be similarly employed.

Isthmic Spondylolisthesis

As mentioned earlier, the basic lesion in this group is a stress or fatigue fracture in the pars interarticularis which allows for the forward displacement of the superior vertebrae. The elongation of the pars, which forms the basis for the subtype B group, most probably results from the stretching of the pars which occurs during the healing process following repetitive stress fractures.

Etiology

There are two main etiological factors which predispose an individual to developing isthmic spondylolisthesis. The concept of a congenital component in the etiology of the isthmic group has been well documented in the medical literature^{12,13,14}. This theory was first suggested by Rothman¹³ after CT scans of patients with

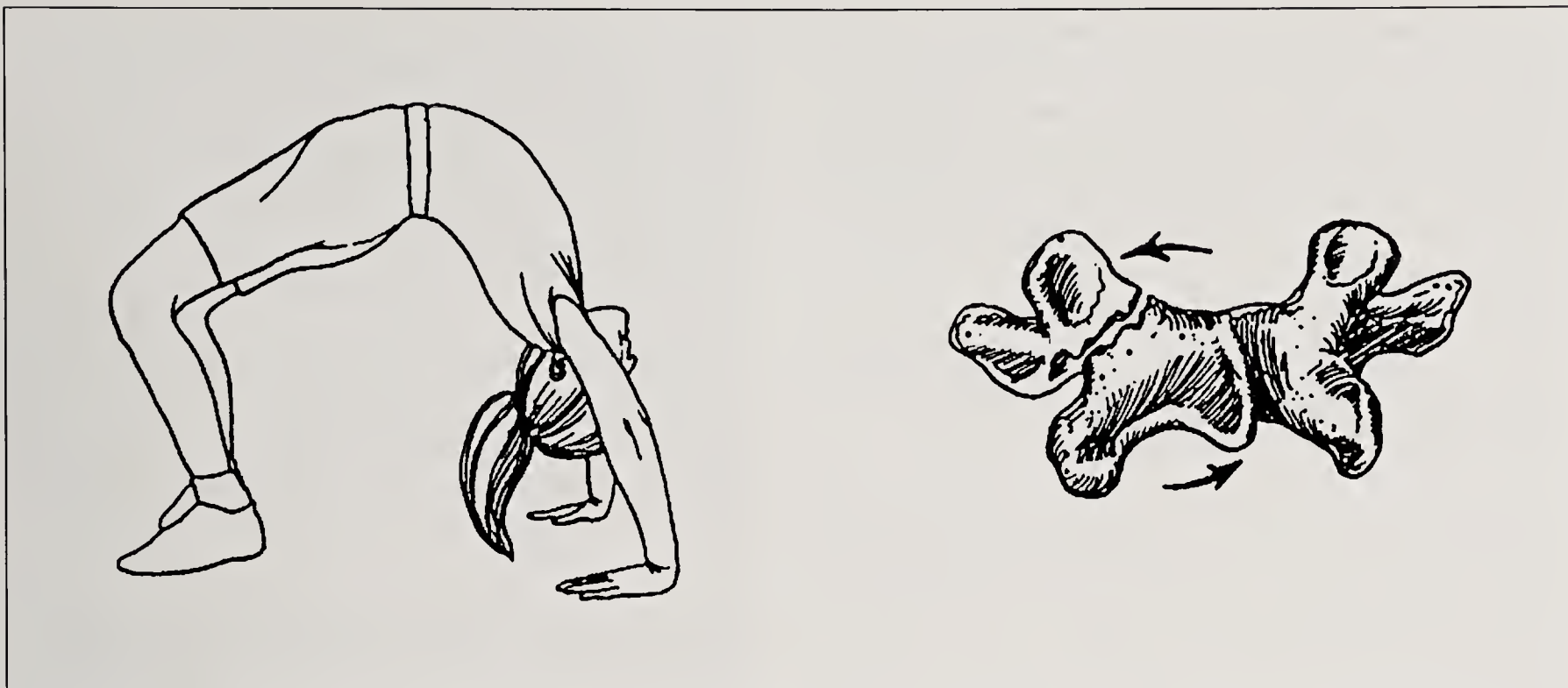


Figure 4 : Repetitive extension and rotation as a mechanism of a pars fracture in a gymnast. (Adopted with permission from reference #5)

isthmie spondylolisthesis revealed hypoplasia of the superior facet joints of S₁. Furthermore, the incidence of other congenital spinal defects such as spina bifida in this group was found to be approximately 30%^{12,14}. In addition, the familial incidence of spondylolisthesis ranges from 25%-70%¹⁴, giving additional credibility to a theory of genetic causation.

Although severe trauma has been postulated as a cause, the most common mechanical cause seems to be repetitive flexion-extension activity, accompanied by rotation, in a young athlete¹⁵. Repetitive flexion¹⁶, combined flexion-extension¹⁷, and hyperextension-rotational¹⁸ stresses have all been proposed as causative to the development of a pars fracture. The very high incidence of pars fractures among young gymnasts supports the hyperextension/rotation theory (Figure 4). It seems that when the athlete is in a position of hyperextension, the L₅-S₁ facet joints are locked and the subsequent rotational stresses are directly transmitted to the pars⁵.

Prevalence

Isthmic spondylolisthesis occurs in the lumbar spine, most commonly at the L₅-S₁ level in 82%, L₄-L₅ level in 11%, and at other levels in 7%⁵. There also seems to be a sex and race difference with males being affected twice as often as females and whites more often than blacks⁵. The overall prevalence of isthmie spondylolisthesis in the general population is 5.4%¹². The highest prevalence, however, occurs in young athletes with the incidence in this group ranging from 11% to 50%¹⁹. The athletes most at risk to developing isthmie spondylolisthesis are weight lifters and gymnasts with the incidence in these groups ranging from 30% to 50%¹⁹.

Natural History

The natural history of isthmie spondylolisthesis has been studied for many years, however, few studies described the natural history of this disorder into late adulthood. One prospective study conducted by Frederickson (1984) was able to answer some very important questions regarding the presentation of this clinical entity in patient into early adulthood¹², but fell short with respect to the evaluation of the disease into the later years of life. Nevertheless, some of his findings are of importance. It has been shown that isthmie spondylolisthesis does not exist at birth. Frederickson found that the incidence of spondylolisthesis at the age of 6 years to be 4.4% and increased to 6% by adulthood¹². These results were similar to those of other studies. None of the children in the study who developed a pars defect while under observation complained of any discomfort, and patients who developed progression of the slip were pain free. Correlation between the degree of slip and the degree of symptoms have never been shown to correlate in any study to date. Thus, patients with a high degree of slip, even 100% displacement, can be symptom free and lead normal lives.

Wiltse²⁰ found that 5% of adult patients examined because of low back pain had a pars defect. Furthermore, Colonna²¹ demonstrated that in 50% of adult patients presenting with symptomatic spondylolisthesis the actual cause for their back pain could be attributed to the pars defect. In other words, no other cause for their pain could be found.

Nevertheless, these figures are puzzling since the development of a pars defect in children has been shown to be asymptomatic¹². Thus, it remains a mystery why adults

so often present with symptoms attributable to a pars defect if this lesion has existed numerous years. Wiltse²², Macnab²³, Farfan²⁴ and others believe that the source of back pain in adult patients with isthmic spondylolisthesis is most often the result of accelerated degenerative changes. Farfan²⁴ showed conclusively that degeneration of the disk above the defect was intimately related to this clinical entity in adults. The use of discography to evaluate this potential cause of pain in patients with isthmic spondylolisthesis may be of benefit⁵, but is still very controversial in the literature.

Though children and adolescents are at an increased risk for further slip, increase in slippage after adulthood is very unusual. Hence, there is no spinal instability²⁵. Furthermore, it seems that the degenerative changes in the spine of adults tend to stabilize the spondylolitic process, except in the degenerative form. The preceding two points have been well documented in the literature reviewing the stability of spondylolitic lesions. Thus, patients presenting to primary care physicians with a spondylolitic lesion and symptoms of chronic, degenerative back pain need not be referred on an urgent basis to specialists for evaluation. Unfortunately, the opposite is often the case.

Treatment

Since the progressive olisthesis in adults is not of clinical concern, the principles of treatment in symptomatic spondylolisthesis in adults focus on pain control. Patient education in terms of the natural history of their illness, emphasis on proper body mechanics and reassurance may be of tremendous benefit in preventing the development of chronic pain syndromes. Initial treatment focuses on various conservative measures for at least 4-6 months. Exercise programs focusing on a flexion regime and abdominal strengthening have decreased pain and the time off work in symptomatic patients²⁶. Furthermore, Steiner and Micheli showed excellent results in patients with a Grade I lesion or less using a modified Boston brace and exercise program²⁷. Other conservative measures such as traction, manipulation, NSAIDS, and facet joint injections may be of benefit but have never been evaluated in clinical trials.

If conservative therapy fails and the pain becomes intolerable, surgery may be considered as a treatment option. Every effort should be made to manage patients with back dominant pain by non-surgical methods. Once surgery is considered as the only alternative, the levels to be stabilized should be L5-S1 and possibly L4-L5 if a significant of degenerative disease exists at that level⁵. Although many procedures have been advocated in the past, including removal of the posterior loose segment,

posterior fusion in situ, posterior decompression and fusion, spondylectomy, combined anterior and posterior fusion, transpedicular fixation combined with decompression seems to be the treatment of choice in Canada. Fusion rates for this procedure vary depending on the number of levels fused, but, according to Yasiro, are approximately 95% for a single level fusion²⁸. Recently, Kim²⁹, McGuire³⁰, and Ricciardi³¹ have all demonstrated excellent clinical results using pedicular fixation in combination with a laminectomy and L5 nerve root decompression. Overall, the risks of reduction of the deformity in the adult seem to outweigh the benefits⁵.

Degenerative Spondylolisthesis (DS)

As discussed above, the olisthesis seen in the degenerative spondylolisthesis results secondary to severe degenerative changes in the facet joints and intervertebral disks.

Prevalence

The exact prevalence of degenerative spondylolisthesis is uncertain. Farfan²⁴, in the examination of autopsy specimens, estimated the prevalence to be about 4%. The lesion occurs about 5 times more commonly in females, and is rarely seen in those under forty years of age³². Furthermore, the lesion occurs 6-10 times more frequently at the L4-L5 level than either the L3-L4 or L5-S1; other levels are rarely involved³³. Patients with this type of spondylolisthesis usually present with a very small slip which may progress, but seldom exceeds 30% displacement³³.

Etiology

Although the precise etiology of degenerative spondylolisthesis has not been fully described, it is believed that the tendency of this condition to involve the L4-L5 preferentially is of etiological significance. It is likely that the degenerative changes in the spinous ligaments and intervertebral disks combined with osteoarthritis of the facet joints may shift the spinal axis of rotation closer to the region of the facet joints thereby increasing the stress load at this level³⁴. Rosenberg outlined many intrinsic mechanical factors of the spine which increase the stress load on the facet joints and the disk of the L4-L5 level³². It is likely that both the intrinsic architecture of the spine, and the degenerative changes in the disk and facet joints seen as part of the aging process, contribute significantly to the development of the slip.

Clinical Presentation

As was the case in the isthmic group, the degree of slip-page observed radiologically does not correlate with clinical findings – people with high grade slips are often asymptomatic. Generally, patients may present with back and/or leg pain, or with intermittent claudication. Brown and Lockwood found the 5% of their patients presenting with low back pain showed radiological evidence of DS⁵. In addition, of their patients with evidence of DS, 78% presented with an element of low back pain. The cause of the back pain is most likely secondary to facet joint OA. Patients with DS can also present with predominantly leg pain, with or without back pain. This presentation accounts for 42% of cases⁵ and is likely secondary to a L4-L5 disk protrusion resulting in direct pressure on the L5 nerve root. Furthermore, patients may present with intermittent claudication. Intermittent claudication is characterized by leg pain brought on by walking, relieved by rest and aggravated by a lordotic stance. It is also important to note that careful examination of the hips is very important since osteoarthritis of the hips is extremely common in this age group and may often be the source of the back pain.

Treatment

The various conservative modalities available to the clinician have already been discussed. These modalities are often of tremendous benefit in patients with DS – especially in those presenting with predominately low back pain. The need for surgical treatment following unsuccessful conservative treatment has been reported to be approximately 10%-15%³². The most common indications for surgery are radiculopathy or spinal stenosis, not back pain.

As mentioned earlier, careful evaluation of patients in preparation for surgery is essential. A CT myelogram, or MRI, as well as a careful medical evaluation are essential. The importance of surgical decompression in surgical candidates is widely accepted, however, the extent of decompression is controversial. Rosenberg³³ originally advocated decompression to only remove enough bone to decompress the nerve root on the symptomatic side. Because of poor results, Rosenberg later supported extensive decompression, but this approach often resulted in increased instability and slipping. Many have shown good clinical results with partial laminectomy and partial medial facetectomy⁵.

Hanley³⁵ and Frymoyer³⁶ proposed that because the deformity in DS includes a rotational element, a fusion procedure is indicated. Pedicular fixation devices correct both the translational and rotational deformities of the

spine and are therefore receiving a great deal of attention among researchers. Unfortunately, the use of pedicle screw systems have been the subject of controversy in the USA. Presently, a decompression procedure combined with fusion of L4-L5 using pedicle fixation screws is the treatment of choice in Canada.

Conclusion

Up to 10% of adult patients suffering from chronic back pain may show radiological evidence of isthmic or degenerative spondylolisthesis^{20,24}. Whether adult patients show evidence of isthmic or degenerative spondylolisthesis, the source of their back pain is most often the result of degenerative changes in the disks or facet joints. The concerns of further olisthesis and subsequent neurological compromise are unfounded. The initial management of these patients should include mild analgesics combined with an aggressive physiotherapy program for no less than 4-6 months and every effort should be made to treat these patients non-surgically.

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The Role of Prostate Specific Antigen in Screening for Prostate Carcinoma

Vincent Chan, B.Sc. (9T6) and Risa Freeman, MD



Abstract

Prostate cancer is the most common malignancy afflicting Canadian men today. Furthermore it is the second most frequent cause of death among men. Very little is known about the pathogenesis of prostate cancer and the screening for this condition using prostate specific antigen (PSA) is currently the subject of much debate. Screening for prostate cancer using PSA is a simple and operator-independent test, however, the sensitivity and predictive value of the PSA screening test are low. These facts, coupled with the unproven effectiveness of treatment for prostate cancer and the lack of evidence suggesting that either life expectancy or quality of life are improved by regular screening, do not justify performing routine PSA screening tests. The psychological burden on the patient who may have to live with the cancer cannot be overstated. Allowing the patient to make an informed choice is therefore strongly encouraged.

Goal

The goal of this review is to evaluate the usefulness of prostate specific antigen (PSA) as a screening tool for prostate cancer in asymptomatic adult men. This evaluation has been facilitated by the use of well-established criteria for the acceptability of screening tests and by reference to published data. Recommendations will be drawn from discussion of the scientific evidence with consideration of the effects on the individual patient and on the community. This review will be of special interest to family physicians and practitioners who attend to male patients over 50 years of age.

Relevance

The use of PSA to screen for prostate cancer has been widely publicized in recent years. Unfortunately, the public has not been well-informed of the nature of this test. Lack of understanding of the disease itself has also

led to immense anxiety for many men as they age. Moreover, within the medical community, the use of PSA for screening purposes is tremendously controversial. There is conflicting evidence as to the utility and cost-effectiveness of PSA as a screening test and there has been additional controversy around the interpretation of test results. The family doctor, therefore, plays a vital role in the application of scientific evidence, albeit controversial, to everyday practice and patient education.

Methodology

This literature review was conducted by a MEDLINE search. MeSH explosions were done on "prostate-specific antigen" and "screening". Limits included "randomized controlled trial", "case controlled trial", and "clinical trial". Text words used included "natural history" and "cost effectiveness". Additional information was gathered from the Canadian Task Force on the Periodic Health Examination.¹

Results

A population-based screening program must satisfy several criteria.² This article will discuss PSA in the context of these criteria:

1. Diseases for which screening is used should be important health problems.

Prostate cancer is the most common malignancy in males, representing 22% of all cancers in Canadian men.³ One in every ten men is diagnosed with prostate cancer in his lifetime.³ The estimated number of new cases in Canada for 1995 is 6,100.³ The prevalence of histologic cancer is age-dependent: ranging from 15% to 30% in men over age 50, and from 60 to 70% by age 80.⁴

Prostate cancer is the second most frequent cause of death from cancer among men in Canada representing 12% of all male cancer deaths.³ One in every 26 Canadian men die from prostate cancer.³ The estimated number of deaths due to prostate cancer in Canada in 1995 is 4,200.³ Seven percent of those who harbour the cancer will die of the disease.⁵ Death from prostate cancer ranks third in terms of potential years of life lost from cancer among Canadian men.⁶

It is important to note that, although prostate cancer is prevalent, 90% of men over age 65 with the disease remain asymptomatic.⁷

2. The natural history of the disease should be thoroughly understood.

Complications from untreated prostate cancer can include obstructive uropathy with renal failure, spinal cord compression secondary to metastatic disease, disseminated intravascular coagulation, pathologic fracture secondary to bony metastasis, and death. Despite the fact that complications from the disease are well-known, there is no clear understanding of the natural history of prostate cancer. Among those who have histologic evidence of cancer, it is not possible to predict who will progress to suffer or die of the disease. Level of PSA, tumor size, and other prognostic indicators fail to correlate accurately with final outcome.

3. A screening test should have high sensitivity and specificity; screening must be safe, and rapidly applied.

Characteristics of the test are listed in Appendix 1. 4 micrograms/Litre is the most commonly used cut-off value, although recommendations range from 3 to 10^{8,9}.

Measurement of PSA involves a simple blood test. The results are more objective than those obtained by other screening tests such as digital rectal examination (DRE) or transurethral ultrasound (TRUS).

4. It is important to compare control and screened groups at regular intervals to establish whether the screening procedure and subsequent investigations have any greater effect than just regular observation of the control groups

To date, there is no randomized controlled trial examining the effect of PSA screening on prostate cancer morbidity and mortality. The National Cancer Institute in the United States of America has recently initiated a large controlled clinical trial. Lead and length time bias are important issues in such trials.

5. Facilities for diagnosis and treatment should be available and effective noncontroversial treatment for patients with confirmed disease should be available

Pathology is the gold standard and is required for definitive diagnosis. Tissue samples are obtained through transrectal/transperineal needle biopsy or sampling from transurethral resection. Risks associated with biopsy include prostatitis, epididymitis, and hematuria.

Treatment of prostate cancer depends on staging (Appendix 2). All of the treatment modalities except watchful waiting are associated with significant risks of complications. Ironically, there is *no* clear net benefit for

any therapy (including no therapy) before the cancer reaches Stage C.^{10,11,12} There is also no evidence that treatment in the asymptomatic phase is superior to watchful waiting.^{13,14}

The majority of cases found by any screening method are diagnosed at Stage B.^{8,15} Without any form of screening, the majority of cases are diagnosed at Stage C or beyond.⁸

6. Comparing the costs and efficiency of various screening methods for a disease are essential for achieving maximum benefit for minimum cost

There have been few formal attempts to evaluate the cost-effectiveness of PSA screening and existing results conflict. One study shows that PSA screening increases cost dramatically while leading to poorer health outcomes.¹⁶ In another study, the authors suggest that PSA testing in addition to digital rectal examination (DRE) is reasonable in terms of the number of carcinoma identified.¹⁷ Although the cost of a single PSA test is low (\$15), the cascade of actions resulting from a positive value are very costly¹⁸. In fact, the Ministry of Health of Ontario has decided to delist the test from the Schedule of Benefits.

It has been suggested that based on the information available today, the most thorough and cost-effective method for detecting early prostate cancer is the combined use of serum PSA determination and digital rectal examination.¹⁹ Transrectal ultrasound should be used to follow up on an abnormal PSA or DRE.

Discussion

Without any form of screening, more than 50% of prostate cancer patients have reached the stage of incurable disease when the cancer is first diagnosed.⁸ Although it is well documented that the use of PSA alone may facilitate early detection^{20,21} and therefore may increase the chance of cure, changes in mortality and morbidity cannot be inferred. There is no evidence that the mortality, morbidity, and natural history of the disease are favourably altered by earlier detection and treatment. Hence, the most difficult issue in evaluating the effectiveness of PSA screening stems from the lack of data from randomized controlled trials. Evidence from these trials is particularly important as the biological behaviour of the disease is unclear. However, lack of evidence *at this point* does not confirm that screening with PSA is valueless. As one author points out, "Is a mass screening test innocent until proven guilty or guilty until proven innocent?"²²

All completed studies in this area are cohort studies. Unfortunately, these tend to suffer from a lack of assessment and follow-up of patients with a sub-threshold PSA (due to the fact that the gold standard in assessment is biopsy, and the fact that the follow-up requires long periods of time). As a result, the quoted values for the sensitivity and specificity of PSA are estimates. The low sensitivity renders the test undesirable as a screening test since a large number of true cancers would be missed. Although PSA is prostate-specific, it is not cancer-specific. PSA is significantly elevated with transrectal ultrasound, biopsy or resection of the prostate, prostatitis, benign prostatic hypertrophy, and renal failure.

The positive predictive values quoted in the literature also suffer from selection bias: patients suspected by their primary care physicians of having cancers are more likely to be referred to a urologist for investigation and thus may be over recruited by the studies that generate these figures. More importantly, the low positive predictive value would create a large number of false positives that would result in unnecessary, invasive tests. Also, since only an estimated 15% of asymptomatic patients have a PSA greater than 4 micrograms/L, the yield is at most 5%. In one study, the positive predictive value was found to be only 8%²³, rendering PSA testing valueless as a screening tool.

When a clinician reports a positive screening PSA to a patient, several difficulties manifest themselves:

- 1) most of the cancers detected by a screening PSA are at Stage B,
- 2) there is no therapy of any benefit for cancers at Stage B,
- 3) all the treatment options are associated with complications, and
- 4) should the patient decline treatment, there is no reliable prognostic factor in deciding whether to follow him up closely or not.

Thus, the dilemma that a positive PSA brings relates to further investigations and treatment.

Lastly, studies of cost-effectiveness have so far only assessed disease curability and not a changes in mortality or morbidity. The psychosocial burden of the disease is also difficult to assess.

Recommendations of Others

The Canadian Task Force on the Periodic Health Examination states that there is insufficient evidence to include PSA screening in the periodic health examination of men over 50 years of age. This recommendation

is made on the basis of low positive predictive value and the known risk of adverse effects associated with therapies of unproven effectiveness (D recommendation). The Canadian Cancer Society, the U.S. Preventive Services Task Force and the National Cancer Institute in the United States also do not recommend PSA for routine screening.

Currently, the Canadian Urological Association supports early detection. It recommends that men between the ages of 50 to 70 should have an annual PSA (or DRE); in those with a positive family history, the recommended age for the commencement of screening is 40 years. The American Urological Association and the American Cancer Society endorse similar recommendations.

Appendix 1	
Serum PSA Level as a Screening Tool for Prostate Cancer – Test Characteristics At PSA greater or equal to 4 micrograms/L ²⁴ :	
Sensitivity	71%
Specificity	75%
Positive predictive value	37%
Negative predictive value	91%

Conclusions and Recommendations

On balance, the evidence available at this point appears to discourage the use of PSA as a screening tool. Arguments that oppose the use of PSA as a screening tool for prostate cancer are based on the lack of understanding of the natural history of the disease, low sensitivity and positive predictive value of the test, known risk of complications from treatments of unproven effectiveness, and the high cost of confirmatory investigations. Arguments in favour of screening include the high prevalence and possible lethality of prostate cancer, ease of performing the test and objectiveness of the result. Ultimately, the effect of PSA screening on mortality and morbidity must be proven by randomized trials.

A physician must apply scientific evidence and demonstrate prudent clinical judgement in order to best serve the population affected by prostate cancer. Beyond the biological side of the disease, the psychological burden on any individual of living with a possible cancer and not taking any action cannot be overstated and can profoundly affect perceived health and even sexual function. Therefore, patients who request screening in order to allay their fears should be met with an informed discussion of the test's merit so that they can make an informed choice. Patient education in the form of pamphlets, such as those published by the Canadian Cancer Society, are important tools that may enable patients to make decisions regarding their physical, as well as psychological, health.

Appendix 2				
Prostate Cancer – Staging and Current Treatment ⁷				
Stage	Description	Treatment	15-year survival (%)	Main complications
A	Cancer confined to the organ with no palpable nodule	watchful waiting	normal	N/A
B	palpable nodule confined to the gland	radical prostatectomy/irradiation	35-60	Surgery: impotence (20-50%), stricture (12%), incontinence (1 to 10%), and death (1%) Radiation: cystitis and proctitis, impotence (33% initially and incidence rises with time), incontinence (6%), stricture (5%), bowel injury (2%), mortality (0.2%)
C	local extension	irradiation	20-30	As above
D	distant metastasis	palliative	0-10	N/A

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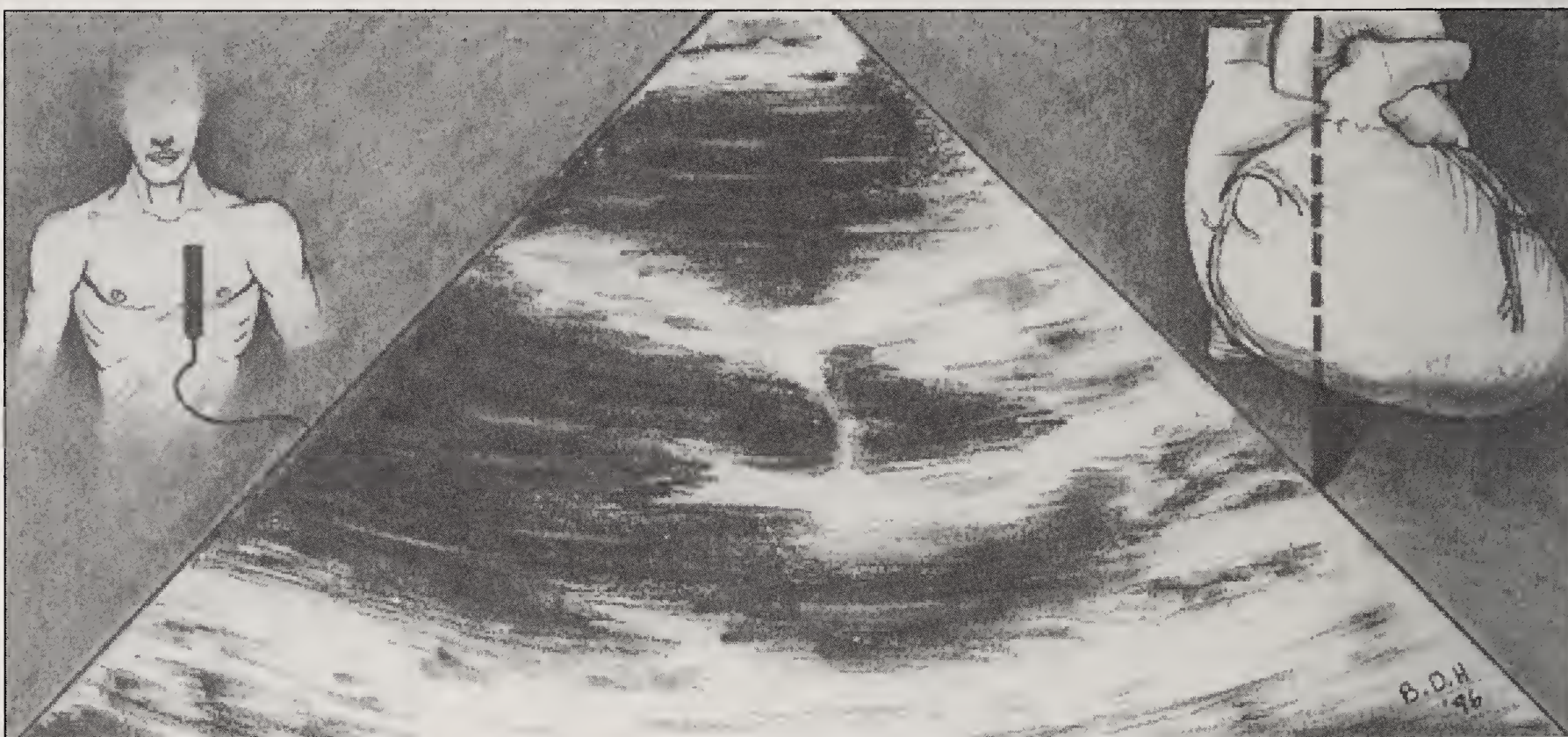


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Indications and Clinical Utility of Emergency Ultrasonography

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BRYCE HOUGH

Abstract

In an era of cost-containment, outcomes research and clinical practice guidelines are becoming important tools in medical practice. Medical imaging is an important area in this regard because of the high-volume and high-cost associated with its role in medicine. In this retrospective study, we examined the indications and clinical utility of emergency ultrasound examinations as ordered under present standards of practice.

The records of 64 patients referred for same day or next morning scans during the study period were reviewed. The pre-referral diagnoses for which emergency ultrasounds were ordered conformed well to documented clinical scenarios for which an ultrasound scan is valid and indicated. Clinical utility of the scans was high for specific clinical diagnosis queries. For patients referred without a clinical diagnosis, the scans had a low utility (15%). Several limitations to the retrospective methodology, which are addressed in the discussion, are important to consider. Given these limitations, we feel that the area of non-specific referrals merits further prospec-

tive investigation. At present, however, based on our findings we do not have evidence to believe that clinical practice guidelines would further optimize patient care in this setting.

Introduction

Health care systems throughout North America are under considerable pressure to control costs and improve efficiency. In Canada, with a single-payer model of health care delivery, the pressures for change are largely due to heavily indebted governments. In the United States, the growing dominance of health maintenance organizations over traditional third-party indemnity insurers has brought about careful scrutiny of medical expenses¹. In this relatively new search for efficiency, rigorous analysis of new and existing medical practices is becoming commonplace. Current analytic approaches include thorough assessment of innovative medical technology before implementation, demands for evidence before instituting new therapy, and the identification of inappropriate utilization of health care resources².

In particular, utilization is examined by considering indications for use, measures of clinical utility, and impact on patient outcomes. Where inappropriate utilization is found, one strategy is to implement clinical practice guidelines for physicians³. Such guidelines prescriptively limit situations under which a test, for example a CT scan, can be ordered. Practice guidelines aim to conform medical practice with what is deemed most effective, but in the process limit physician autonomy⁴.

At the present time, ultrasound examinations are among the most frequently requested radiologic test for patients in the emergency department. Primarily used for the detection of abdominal and pelvic disease, other emergent uses include imaging of peripheral veins and scrotum. Considerable controversy exists as to whether or not all scans ordered by emergency department staff are indicated. It is also not clear whether all scans provide clinically useful information given the frequency with which they are ordered, that is, whether sufficient preselection of patients is taking place to ensure a high yield of useful scan findings.

In this study, we were concerned with the utilization of ultrasonography for patients referred for same day or next morning scans from the emergency department. Our objectives in conducting this study were to determine first, whether scans were being ordered for appropriate clinical indications; second, to assess the clinical utility of scan results; third, to provide an indication regarding the necessity of further investigations and possible practice guidelines for this clinical setting.

Methods

The study period under consideration was the month of February 1995. The setting was The Toronto Hospital, General Division, a large tertiary care, university affiliated teaching hospital. All case records of patients referred from the emergency department for same day or next day ultrasounds were retrospectively reviewed. A retrospective methodology was chosen as a suitable first step in the investigation of the questions under study.

Patient records were reviewed for demographics, presenting signs and symptoms, clinical (pre-referral) diagnosis, ultrasound findings, post-ultrasound diagnosis, further imaging, and subsequent hospitalization or surgery.

Based on ultrasound findings, it was assessed whether the ultrasound scan confirmed the queried clinical diagnosis, excluded the queried clinical diagnosis, found unsuspected pathology, or was equivocal and non-contributory. A scan was considered *clinically useful* if it confirmed the diagnosis, excluded the diagnosis, or detected unsuspected pathology. A scan was considered *not clinically useful* if it was equivocal or showed no pathology when no clinical diagnosis was suggested on referral (eg. Abdominal Pain Not Yet Diagnosed (NYD) - a non-specific referral diagnosis). Clinical utility was defined as the number of clinically useful scans for a given clinical scenario expressed as a percentage of the total number of scans performed for that clinical scenario.

Results

In the month of February 2,239 patients presented to the emergency department at The Toronto Hospital, General Division. Of these, 68 patients had ultrasound examinations the same day of presentation to emergency or early the next morning. Four patients had incomplete medical records and had to be excluded from the study.

The subject profile is shown in Table 1. For these 64 patients, abdominal pain in some form was the most common presenting symptom (50%). Other frequent symptoms were vaginal bleeding, thigh or leg pain or swelling, and flank pain. Table 2 shows the percentage of patients with various presenting symptoms.

TABLE 1: Subject Profile

	MALES	FEMALES
Number	21	43
Average Age	63	42

TABLE 2: Presenting Symptoms

PRESENTING SYMPTOM	% OF TOTAL
Abdominal Pain	30
Thigh/Leg Pain/Swelling	13
Vaginal Bleeding	11
Right Lower Quadrant Pain	8
Epigastric Pain	6
Suprapubic Pain	6
Pelvic Pain	3
Other	22

A total of 102 ultrasound scans were performed on 64 patients. Abdominal scans were performed on 67% of patients, pelvic scans on 50% of patients, transvaginal scans on 22% of patients, peripheral venous doppler scan on 14% of patients, scrotal scans on 5% of patients, and neck scans on 2% of patients.

The assessment of ultrasound clinical utility is shown in Table 3 according to the various clinical (pre-referral) diagnoses made by the emergency physician. The "Biliary Tract Disease" category included cholecystitis, cholangitis, cholelithiasis, and choledocholithiasis. The "Other" category included pre-referral diagnoses made only once. These are small bowel obstruction, ascites, hepatomegaly, testicular torsion, PID, vaginal bleeding, neck swelling NYD, and pneumonia.

Of the 64 patients in the study, approximately half of the patients (53%) were admitted to hospital, with an average stay of 9 days. However only three went on to have further imaging. Two patients, diagnosed with renal calculi, underwent intravenous pyelograms, and one patient, with

TABLE 3: Clinical Utility

DIAGNOSIS	NO.	CONFIRM	EXCLUDE	SIGN. PATH	NON-CONT.	UTILITY
Abdominal Pain NYD	11	0	0	2	9	0.18
Biliary Tract Disease	9	2	3	0	4	0.56
Renal Colic	6	4	2	0	0	1.00
DVT	6	1	4	0	1	0.83
Abdo Abscess/Infection	4	0	3	0	1	0.75
Threatened Abortion	4	3	1	0	0	1.00
Appendicitis	4	0	4	0	0	1.00
Ectopic Pregnancy	3	0	2	1	0	1.00
Pancreatitis	3	0	1	0	2	0.33
Suprapubic Pain NYD	2	0	0	0	2	0.00
Testicular Swelling	2	2	0	0	0	1.00
Ascites	2	0	1	0	1	0.50
Other	8	3	0	0	5	0.38
TOTALS	64	15	21	3	25	0.61

Notes: NYD (Not Yet Diagnosed); DVT (Deep Venous Thrombosis); Abdo (Abdominal).

suspected pyelonephritis, underwent a CT scan and had a subsequent nephrectomy.

Discussion

The field of medical imaging is becoming increasingly influenced by the use of clinical practice guidelines given the high-cost and high-volume associated with imaging tests⁵. Until recently, radiology research has focused primarily on clinical and descriptive studies, with a relative lack of analytical research⁶. With the changing practice climate, examining the contribution of diagnostic interventions is becoming imperative. Such studies provide the impetus for constructing guidelines for the given practice area.

The two components of utilization we sought to assess were the indications used by emergency physicians ordering ultrasound examinations, and whether or not inappropriate utilization, suggested by a low clinical utility of scan results, was taking place.

In assessing the indications for ordering ultrasound examinations, one must ensure that ultrasound has been proven to be valid in the diagnosis of the suspected disease entity. The validity of a test is a measure of the correlation between the test results and the actual presence or absence of disease as measured by a gold standard. Measures of validity include sensitivity, specificity, positive predictive value, and likelihood ratios⁷. If ultrasound is proven valid, then it may be considered to be indicated when the particular disease entity is suspected.

Ultrasound is the preferred imaging modality for the investigation of many abdominal and pelvic disease entities. It has documented validity in the diagnosis of biliary tract disease, pelvic inflammatory disease, threatened abortion, and the detection of abdominal abscesses⁸. In cases of acute flank pain and suspected renal calculus, it has a high

specificity and is thus useful for ruling out disease⁹. Ultrasound has proven valid in the diagnosis of ectopic pregnancy^{10,11} and appendicitis¹². A peripheral venous doppler examination in the case of suspected deep venous thrombosis has a high sensitivity and specificity¹³. Ultrasound has also been validated in the detection of ascites¹⁴, pancreatitis¹⁵, and in imaging testicular masses¹⁶. Thus, for all the specific referral diagnoses in our study (80% of all referrals), there is evidence for the validity of ultrasound.

It is impossible to assess the validity of ultrasound for non-specific referrals since it requires a specific finding to look for and a gold standard with which to compare ultrasound results. However, all of the non-specific referrals were abdominal and pelvic pain presentations and, as indicated above, ultrasound had documented validity in a number of specific abdominal and pelvic disease entities.

As defined previously, the clinical utility of the scan to the emergency physician can be considered high if a significant portion of the time, the results either confirm or exclude the diagnosis or suggest unqueried significant pathology. Our overall results indicate that for specific clinical diagnoses the clinical utility of ultrasound was 73%. Excellent clinical utility (>75%) was found for specific queries of renal colic, abdominal abscess/infection, threatened abortion, appendicitis, ectopic pregnancy, deep venous thrombosis, and testicular swelling. In biliary tract disease (56%), ascites (50%), and pancreatitis the utility was less. However, the majority of scans that were non-contributory in these cases (5 out of 7) were of poor quality and the interpreting radiologist was unable to comment on the presence or absence of disease. Overall, these results suggest appropriate use of ultrasound examinations for specifically queried clinical diagnoses. These findings are consistent with an earlier study which also documented a high clinical utility for these indications¹⁷.

Analysis of non-specific referral categories of "Abdominal Pain NYD" and "Suprapubic Pain NYD" had a low clinical utility of 15 percent. Of 13 referrals of this nature, only two scans revealed significant pathology. In both cases, ultrasound examination detected the presence of an ovarian cyst.

This low yield is as expected by the nature of the referral. When the clinician is unable to suggest a diagnosis based on a thorough clinical and laboratory assessment, it seems unlikely that a scan would detect abnormalities in a significant number of cases. Given this low utility, we think this is an area that requires further investigation prospectively. In a prospective study it would be possible to better characterize the symptomatology at presentation, and follow ultimate patient outcomes in order to assess the utility of these scans.

Limitations

This study has four principle limitations. First, due to the fact that the clinical diagnoses were obtained retrospectively on each patient from the medical record chart, we were unable to ascertain whether or not, in the case of non-specific referrals, the emergency physician had a more specific diagnosis in mind but neglected to record it. This may have led to an overclassification of scans in non-specific referral categories.

Second, the retrospective methodology also increases the possibility of misclassifying scan outcome. It was not possible to know for certain what the emergency physician's opinion of the scan outcome was. That is, we could not be certain what role the scan results played in the physician's decision making. Ideally, assessments of clinical utility are made prospectively with the assessments being provided directly by the physician for whom the scan is performed¹⁸.

Third, considerations of clinical utility are important in utilization reviews, but the ultimate question is whether the scan findings contributed to the overall outcome of the patient. This answer cannot be obtained retrospectively, and is often difficult to obtain prospectively. Given the methodological limitations, we did not seek to answer this question in the present study.

Fourth, we were unable to ascertain the total number of patients who presented to the emergency department during the study period with the symptoms for which scans were typically ordered, but did not undergo ultrasonography. Therefore, we are not able to comment on the degree of selectivity with which emergency physicians ordered scans. Given the high clinical utility of scan results, it is also possible, for example, that more patients might have benefitted from a scan than actually received one.

The above limitations could adequately be addressed in a well-designed prospective study. Such a study would note the symptomatic presentation of all patients presenting to the emergency department during the trial period, identify the clinical diagnosis of the emergency physician before the ultrasound scan was ordered, and ask the emergency physician to comment on the utility of the scan outcome.

The answer to the question of the contribution of ultrasound scans to patient outcome would require an experimental trial methodology with one group of patients receiving the intervention and a second group not receiving the intervention. This is unlikely to be feasible in this practice setting at the present time.

Conclusions

Under present standards of practice by emergency physicians at our institution, the suspected clinical diagnoses for which emergency ultrasound examinations are being ordered conform to accepted clinical indications.

When specific queries are given, the clinical utility of the scans are high (73%) and do not suggest inappropriate utilization. When a patient is referred for a scan without a specific clinical diagnosis, the clinical utility of the scan is low. Given the limitations of the retrospective methodology, we feel that this is an area that merits further investigation prospectively. Based on this present study, however, we do not have evidence to conclude that clinical practice guidelines would further optimize patient care in this clinical setting.

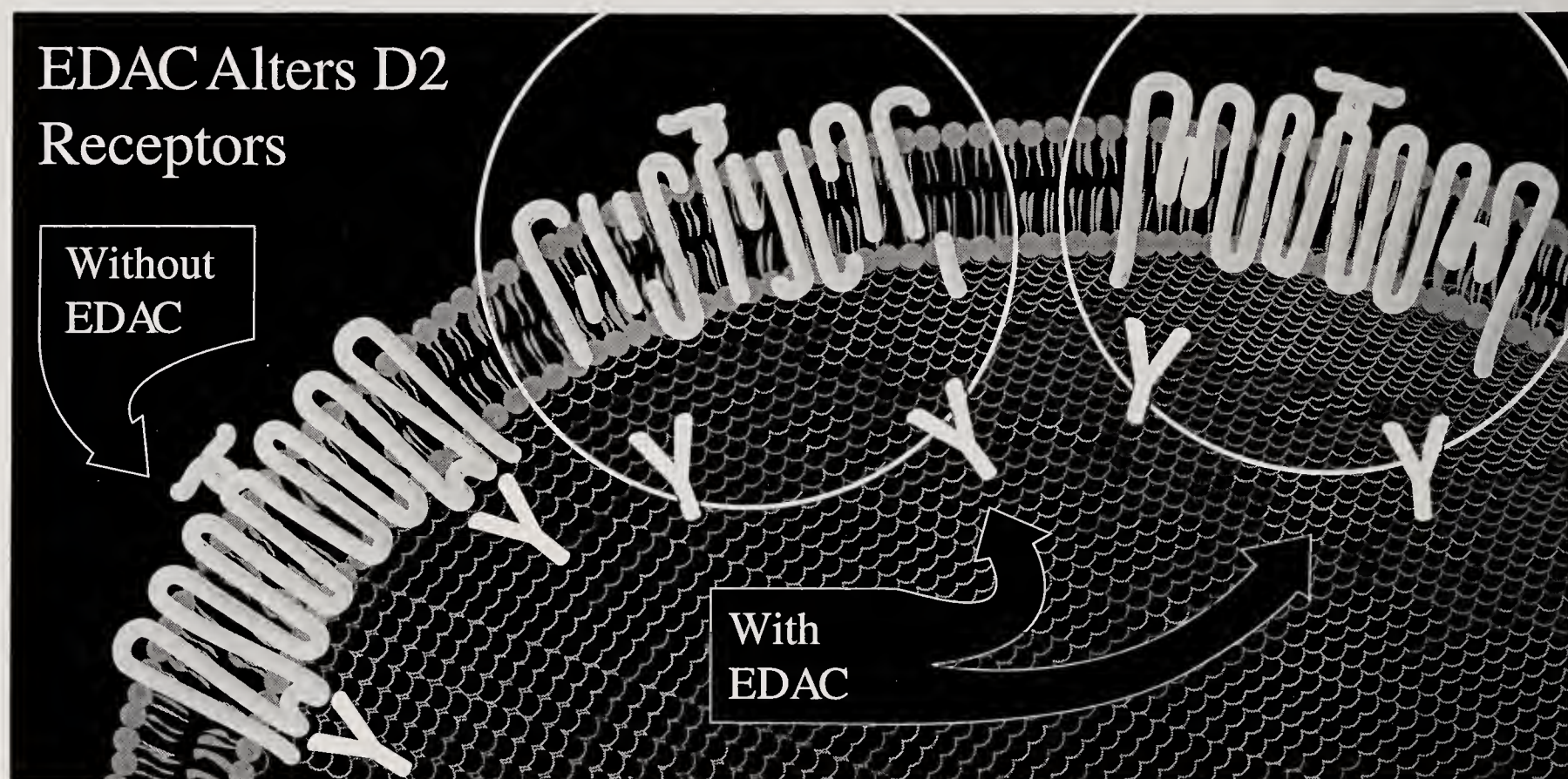
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Biochemical Characterization of D2 Receptor Monomers & Dimers Expressed in Sf9 Cells

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LAURA MAASKE

Abstract

Using immunoblot analysis, a D2 receptor-specific antibody detected the presence of two major immunoreactive species at ~44 and ~93 kDa in Sf9 cells expressing the human D2 receptor, suggesting the presence of D2 receptor monomers and dimers. To study the nature of the biochemical bonds involved in dimerization, D2 receptors were treated with EDAC, a covalent cross-linking agent, and dopamine, an endogenous agonist. Although EDAC did not significantly increase the number of D2 dimers under immunoblot analysis, it did decrease the monomer numbers substantially. When the D2 receptors were treated with both EDAC and D2 drugs such as dopamine and (+)-butaclamol, the

intensity of both bands did not change significantly from EDAC treatment only. Hence, EDAC-treated D2 receptor species do not respond to ligands.

Using [g-³²P] ATP, the D2 receptor species were phosphorylated and discriminated by SDS-PAGE and autoradiography. Under basal conditions, the intensity of the D2 dimer band was substantially greater than under dopamine-treated conditions, consistent with previous reports that the D2 receptor may be intrinsically phosphorylated. Also, we attempted to preserve the phosphorylated D2 receptor with okadaic acid, a phosphatase inhibitor. Using radioligand binding analysis, okadaic acid does not significantly affect the binding characteristics of the D2 receptor, as assessed by [³H]-YM-09151-2.

Abbreviations

EDAC	(1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide)
Sf9	(<i>Spodoptera frugipeda</i>)
DA	(Dopamine)
D2	(Dopamine D2 _L receptor)
SDS-PAGE	(Sodium dodecyl sulphate - polyacrylamide gel electrophoresis)
MES	(4-morpholineethanesulfonic acid)
TBS	(Tris-buffered saline)
PBS	(Phosphate-buffered saline)
PDGF	(Platelet-derived growth factor)
EGF	(Epidermal growth factor)
5-HT _{1B}	(Serotonin _{1B} receptor)

Introduction

Different subtypes of the dopamine receptor have been identified and differentiated pharmacologically and biochemically. The dopamine receptor is divided into two subclasses: the D1-like and D2-like receptors¹. The D1-like receptors include the D1 and D5 subtypes whereas the D2-like receptors include the D2 and its variants, D3 and D4 subtypes^{2, 3, 4, 5, 6}. The D1-like receptor stimulates adenylyl cyclase via G_s, a guanine nucleotide regulatory protein, and activates cAMP-dependent protein kinases. Conversely, the D2-like receptor inhibits adenylyl cyclase via G_i, a guanine nucleotide regulatory protein, phospholipase C activity and voltage-dependent Ca²⁺ current^{7, 8, 9}. Both the dopamine D1 and D2 receptors have been implicated in drug reward¹⁰ and in neuropsychiatric disorders such as Parkinson's disease and schizophrenia¹¹.

Yet relatively little is known about how the dopamine D1 and D2 receptors are involved in drug reward and in neuropsychiatric disorders. To elucidate their roles, further biochemical and pharmacological characterization of the D1 and D2 receptors is needed. In this study, we examined the biochemical characteristics of the D2 monomer and dimer species.

A previous study proposed the presence of both D2 monomer and dimer species based on the observation that under denaturing SDS-PAGE and immunoblot analysis, the D2 receptor-specific AL-26 antibody detected the presence of two major immunoreactive species at ~44 and ~93 kDa in Sf9 cells expressing the D2 receptor¹². Since the two immunoreactive species are also found in the membranes of other mammalian cell lines expressing the D2 receptors¹³, they postulat-

ed that the higher and lower molecular mass proteins probably represent a D2 dimer and monomer, respectively. Radioligand binding analysis yielded a similar interpretation: the presence of two D2 receptor species. Using the D2 antagonists [³H]-spiperone and [³H]-YM-09151-2, radioligand binding analysis revealed two significantly different receptor densities in the same membrane preparation¹². This differential binding of the two D2 antagonists has also been reported in rat and porcine anterior pituitary tissue, postmortem human caudate tissue and in other mammalian cell lines expressing the D2 receptors^{14, 15, 16}. At the time, Seeman et al. interpreted the differential binding as suggesting that YM-09151-2 binds to monomers whereas spiperone binds to dimers¹⁶.

Receptor-receptor interactions have been reported in other types of receptors as well. Incidentally, an intramembrane dopamine D1-D2 receptor interaction has been reported in human post-mortem brain striata¹⁷. The clinical relevance of the interaction is an additive one, each receptor enhancing the other's actions, in the context of psychomotor signs and symptoms^{17, 18}. In other G protein-linked receptors such as the muscarinic M1 and M2 receptors expressed in Sf9 cells, 5-HT_{1B} receptors in Sf9 cells, and the cloned metabotropic glutamate receptor expressed in hamster kidney cells, receptor dimerization may be a post-translational event^{19, 20, 21}. In the platelet-derived growth factor receptors, receptor dimerization occurs when PDGF binds to a receptor which is followed by autophosphorylation of tyrosine residues²².

Although documented to exist, the biochemical characteristics of the D2 monomer and dimer species remains to be clarified. To discern the nature of the bond involved in receptor dimerization, we used EDAC, a covalent cross-linker agent used by Cochet et al. to stabilize the EGF dimer, to detect the presence of polar bonds²³. In the D2 receptor amino acid sequence, there are consensus sequences in the third putative intracellular cytoplasmic loop which are recognized by phosphorylating enzymes. To investigate whether receptor phosphorylation is connected to D2 dimerization, membranes expressing the D2 receptor were treated with dopamine in the presence or absence of EDAC; EDAC was used to prevent the possible break down of the dimer into monomers. Ng et al. demonstrated that in the absence of agonist the D2 receptor is phosphorylated¹². Furthermore, we treated the Sf9 cells, expressing the D2 receptors, with okadaic acid, a phosphatase inhibitor, to examine its effects on D2 receptor densities in the presence or absence of dopamine.

Materials and Methods

Materials

Grace's supplemental medium, fetal bovine serum, gentamycin sulfate, fungizone, goat serum and rabbit serum were purchased from GIBCO (Toronto, Ont.). (+)-Butaclamol, spiperone, YM-09151-2, quinone, (-)-sulpiride, SCH-23390 and MES (4-morpholineethanesulfonic acid) were from Research Biochemicals Inc. (Natick, MA). [^3H]-Spiperone, [^3H]-YM-09151-2 and [$\gamma\text{-}^{32}\text{P}$] ATP were obtained from Du Pont NEN (Boston, MA). Dopamine, anti-rabbit IgG coupled to alkaline phosphatase, leupeptin, benzamidine, soybean trypsin inhibitor and EDAC (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide) were from Sigma Chemical Co. (St. Louis, MO) and Amersham (Arlington Heights, IL). Nitrocellulose was purchased from Schleicher and Schuell. Goat anti-rabbit antibody coupled to alkaline phosphatase and dye reagent concentrate for protein assays were from BioRad (Toronto, Ont.). All other chemicals for gel electrophoresis were purchased from Novex (San Diego, CA). *Spodoptera frugiperda* (Sf9) cells were from ATCC (Rockville, MD). The human D2L receptor was a generous gift from Dr. O. Civelli (Portland, OR).

Construction of the Recombinant Baculovirus

The cDNA clone, encoding the long form of the human D2 dopamine receptor (D2L), was extracted from the pZem 3 vector with *Dra*III and *Kpn*I¹². This fragment was blunt-ended and separated by electrophoresis on soft agarose. The transfer vector pJVETLZ New (a gift from Dr. C. Richardson, BRI) was digested with *Nhe*I and blunt-ended. The cDNA fragment was inserted into the vector by blunt-end ligation and the orientation was verified by sequencing.

Culture of Sf9 Cells

Sf9 cells were cultured in suspension in Grace's insect media, supplemented with 10% fetal bovine serum, gentamycin and fungizone at 28°C. At a density of $1\text{--}2 \times 10^6/\text{mL}$, the Sf9 cells were infected with the recombinant baculovirus at a multiplicity of infection of 2 and harvested at 24 or 48 h after infection. Trypan blue staining showed that the cell viability was ~80% (trypan blue-negative).

Preparation of Membranes

The membranes were prepared at 4°C as previously described by Ng et al.¹² Cells were pelleted by cen-

trifugation at $100 \times g$ for 10 minutes. The pellet was homogenized in 50 mL of cold phosphate-buffered saline (PBS) and centrifuged at $100 \times g$ for 10 minutes twice. The PBS wash removes any possible contaminants. The cells were resuspended in buffer A [5 mM Tris-HCl, 2 mM EDTA buffer] containing the protease inhibitors [10 $\mu\text{g}/\text{mL}$ benzamidine, 5 $\mu\text{g}/\text{mL}$ leupeptin and 5 $\mu\text{g}/\text{mL}$ soybean trypsin inhibitor (pH 7.4 at 4°C)]. The suspended cells were disrupted by Polytron and centrifuged at $100 \times g$ for 10 minutes to pellet unbroken cells and nuclei. The supernatant was centrifuged at high speed ($27,000 \times g$) for 25 minutes to pellet the disrupted membranes (P2), containing the expressed D2L receptors. The P2 was resuspended in buffer A and stored at -70°C.

Using bovine serum albumin as the standard, the protein content was determined by the method of Bradford (BioRad).

Radioligand Binding Assays

Saturation experiments were performed with increasing concentrations of [^3H]-spiperone and [^3H]-YM-09151-2 (10-2000 pM, final concentration), D2 antagonists, to determine the B_{max} or the D2L receptor density of the membranes. The assay was done in duplicate and incubated for 90 minutes at 22°C. The incubation mixture included binding buffer B [50 mM Tris-HCl, 5 mM EDTA, 1.5 mM CaCl_2 , 5 mM MgCl_2 , 5 mM KCL, 120 mM NaCl (pH 7.4 at 22°C)] containing protease inhibitors and ascorbic acid, [^3H]-spiperone, membrane (15-20 $\mu\text{g}/100 \mu\text{L}$ of membrane) and 1 μM (+)-butaclamol (for the non-specific binding points only), as described in Ng et al.^{12, 24} Receptor-bound ligands were isolated by rapid filtration through a Brandel 48-well cell harvester, using Whatman GF/C filters. Filters were washed with 10 mL of cold 50 mM Tris-HCl buffer (pH 7.4), placed in glass vials with 5 mL of Universol scintillation fluid and counted for tritium. All binding data were analyzed by nonlinear least squares regression.

Cross-Linking Dopamine Receptors

Membranes were resuspended in 20 mM MES buffer (pH 7.0), containing protease inhibitors and ascorbic acid, with or without 10 μM of one of the following drugs: dopamine, quinpirole, spiperone, YM-09151-2, (-)-sulpiride, SCH-23390, (+)-butaclamol to a final volume of 1 mL. Tubes were incubated for 45 minutes at 22°C. Afterwards, 15 mM EDAC, prepared in a 100 mM MES buffer (pH 7.0), was added to each tube and incubated for 30 minutes at 30°C²³.

Immunoblot Analysis of Dopamine Receptor Species

Membranes were solubilized in sample buffer [50 mM Tris-HCl, 10% SDS, 10% glycerol, 10% β -mercaptoethanol and 0.003% bromophenol blue, pH 6.5]. Gel electrophoresis was performed with 8-16% or 12% SDS-PAGE gels and the proteins were transferred onto nitrocellulose electrophoretically. The nitrocellulose was washed in Tris-buffered saline (TBS), blocked with 5-10% skim milk powder in TBS buffer, washed with TBS and incubated with anti-rabbit IgG coupled to alkaline phosphatase (diluted 1:20 in TBS containing 1% skim milk powder). Then the nitrocellulose was treated with 0.05% Tween-20 in TBS to remove any non-specifically bound primary antibody. Goat anti-rabbit IgG alkaline phosphatase conjugate, diluted 1:1000 in TBS containing 1% skim milk powder, was used to amplify the primary antibody signal. Afterwards, blots were rinsed in 0.1 M Tris-HCl (pH 9.5) before developing with BCIP/NBT (5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium) substrate (BioRad, ON).

Receptor Phosphorylation in the Presence/Absence of Agonist and/or EDAC

The membranes expressing the D2 receptor were resuspended in 20 mM MES (pH 6.5), containing protease inhibitors and ascorbic acid, with or without 20 mM dopamine and incubated at 22°C for 45 minutes. The membranes were then centrifuged at 4°C at 15,000 x g for 15 minutes and resuspended in 15 mM EDAC-MES (diluted in 100 mM MES buffer, pH 6.5) or 100 mM MES buffer (pH 6.5), containing protease inhibitors and ascorbic acid, with or without 20 mM dopamine. The membranes were incubated at 30°C for 30 minutes and centrifuged at 4°C for 15 minutes at 15,000 x g. The pellet was washed twice with 5:2 Lysis buffer [containing inhibitors] and solubilized for 20 minutes in 10 μ L of 5:2 Lysis buffer (containing 10% glycerol, inhibitors and 0.5% Triton-X). The solubilized receptors were diluted in 20 μ L of 5:2 Lysis buffer containing inhibitors. A 10 μ L aliquot was incubated for 10 minutes at room temperature with or without 2 mM DA. Afterwards, 100 μ M ATP, 410 mM MgCl₂ and 1 μ Ci of [γ -³²P] ATP was added and the resulting mixture was incubated for 10 minutes at 4°C. The reaction was stopped by adding SDS sample buffer and loaded onto 8-16% SDS-PAGE gels for gel electrophoresis. The gel was fixed and dried at 80°C for 1 hour before exposing it on Kodak XAR film with an intensifying screen.

Results

In Figure 1, membranes were treated with or without EDAC and with or without a D2 agonist/antagonist. Immunoblot analysis using the D2 receptor-specific antibody revealed the presence of two major immunoreactive species at ~44 and ~93 kDa in the EDAC-untreated control lane (Lane 1). The D2L receptor is a 444 amino acid protein with a predicted molecular mass of ~44 kDa and therefore indicates that the ~44 kDa band on the immunoblot is the unglycosylated D2L receptor monomer. The ~93 kDa molecular mass band, approximately twice the mass of the monomer, likely represents the D2L receptor dimer. This interpretation is consistent with radioligand binding analysis using two D2 antagonists, [³H]-spiperone and [³H]-YM-09151-2; the radioligand [³H] YM-09151-2 consistently detected a receptor density that was two-fold or greater than detected by [³H]-spiperone in the same membrane preparation, suggesting the presence of two different D2 receptor species (data not shown). In the EDAC-treated membranes (Lanes 2-9), the D2 receptor monomer band was less intense than the the EDAC-untreated membranes (Lane 1). The D2 receptor dimer band, however, was present though it was not significantly different in intensity with the EDAC-untreated condition (Lane 1). Drug exposure (Lanes 3-9) did not cause any significant change in intensity of the monomer and dimer bands, compared to the drug-untreated membranes (Lane 2); their slight difference in intensity is likely due to uneven loading of membranes into the SDS-PAGE.

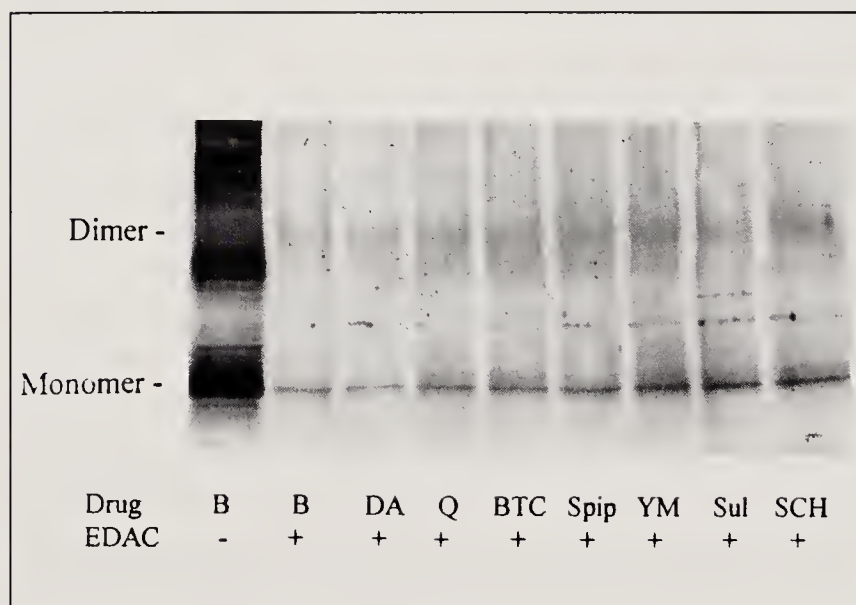


Figure 1. Immunoblot analysis of the D2 receptor species using a D2-specific antibody. Membranes were solubilized in SDS buffer, electrophoresed and electroblotted onto nitrocellulose, and immunoreactivity was revealed with a goat anti-rabbit IgG conjugated to alkaline phosphatase as described in Materials and Methods. Other than Lane 1, all the other lanes represent D2 receptors treated with EDAC. (B) Basal condition; (DA) Dopamine; (Q) Quinone; (BTC) (+)-butaclamol; (Spip) Spiperone; (YM) YM-09151-2; (Sul) (-)-sulpiride; (SCH) SCH-23390.

In Figure 2, autophosphorylation of the D2 receptor was studied under dopamine and/or EDAC exposure. Again, a D2 receptor-specific antibody was used to detect the presence of monomers and dimers. In the control (no EDAC nor dopamine present), a prominent dimer band is visible (Lanes 1 & 2). The dimer bands in the two lanes, however, were of unequal intensity; Lane 1 is darker than Lane 2. In the agarose gel, uneven amounts of membranes were regrettably loaded into the two lanes. In Lanes 3 & 4, neither the monomer or dimer bands are present when the membranes are treated with EDAC only. Exposure to dopamine alone results in a D2 dimer band only (Lanes 5 & 6). And in the presence of both dopamine and EDAC, no immunoreactive species are observed (Lanes 7 & 8).

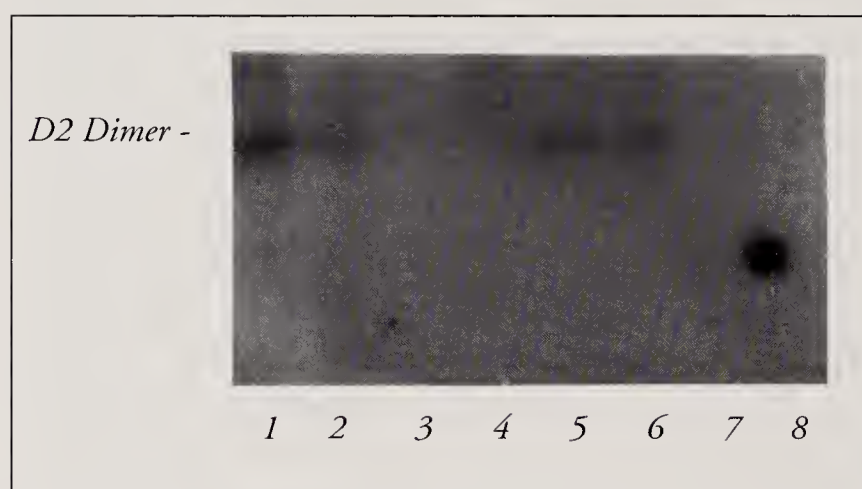


Figure 2. Membranes were exposed to [γ - ^{32} P] ATP. Lane 1 & 2, phosphorylated D2 dimer in basal conditions; lane 3 & 4, membranes treated with EDAC only; lane 5 & 6, phosphorylated D2 dimer under dopamine exposure; lane 7 & 8, membranes treated with both EDAC and dopamine. The autoradiogram is from a 2.5 day exposure.

In Figure 3, saturation isotherms of [^{3} H]-YM-09151-2 and [^{3} H]-spiperone were performed on the same membrane preparation. [^{3} H]-YM-09151-2 and [^{3} H]-spiperone each bound to a homogeneous population of sites with a mean K_D of 191.24 pM and 87.05 pM, respectively. The receptor density of [^{3} H]-YM-09151-2 was 2.35 pmol/mg of protein whereas the B_{max} of [^{3} H]-spiperone was 1.66 pmol/mg of protein. Consistently, saturation isotherms for [^{3} H]-YM-09151-2 yielded a B_{max} twofold or greater than one for [^{3} H]-spiperone in the same membrane preparation (Fig. 3).

Figure 4 shows the saturation isotherms of [^{3} H]-YM-09151-2 binding to the same membrane preparation from Sf9 cells expressing D2 receptors at 72 h after infection. The Sf9 cells were treated with okadaic acid and/or dopamine. The K_D (pM) and B_{max} (pmol/mg of protein) values were 121.80 and 2.27 for basal conditions, respectively, and were 180.07 and 2.13 for okadaic acid treatment, respectively. The K_D (pM) and B_{max} (pmol/mg of protein) values were 185.96 and 3.57 for

dopamine treatment, respectively, and were 232.23 and 3.83 for okadaic acid and dopamine treatment, respectively.

Discussion

Immunoblotting Cross-Linked D2 Receptors

Under SDS denaturing conditions, gel electrophoresis and immunoblotting using a D2L receptor-specific antibody indicated the presence of two protein species at ~44 kDa and ~93 kDa, suggesting the presence of a D2L receptor monomer and dimer species¹². Until now, the biochemical characteristics of the D2 receptor dimer has been largely unknown. To address this question, EDAC, a covalent cross-linker agent, was used. EDAC covalently links free amino groups to carboxyl groups to create a polar bond²³. More specifically, EDAC bridges any lysine side chains with an acidic residue when the two are within the distance of a peptide bond. Therefore, if polar bonds are indeed involved, EDAC should further stabilize and induce D2 dimerization.

On the immunoblot, the monomer bands of EDAC-treated membranes were of a lesser intensity than the EDAC-untreated membranes (Figure 1). Conversely, the intensity of the dimer bands of EDAC-treated membranes were not very different from the control. The

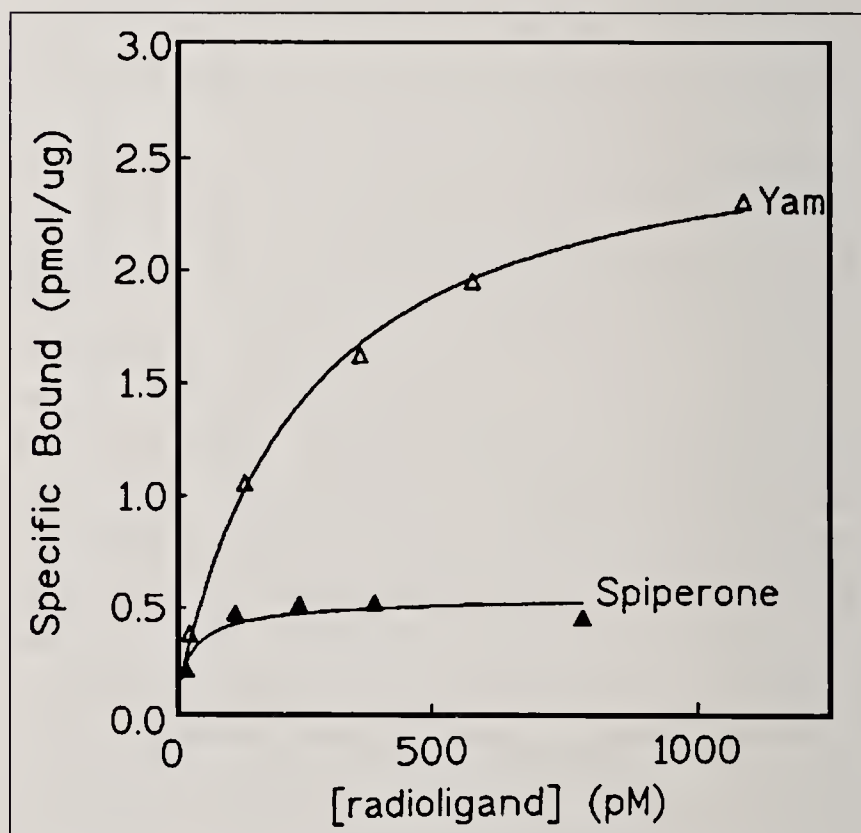


Figure 3. Radioligand binding assay of membranes from Sf9 cells expressing the D2 receptor. Specific radioligand binding was defined as binding inhibited by 1 μ M (+)-butaclamol. Saturation isotherms of [^{3} H] spiperone and [^{3} H] YM-09151-2 specific binding in the same membrane preparation. In this particular assay, B_{max} (pmol/mg of protein) and K_D (pM) are as follows: [^{3} H] spiperone (Δ), B_{max} = 1.66, K_D = 87.05; for [^{3} H] YM-09151-2 ($\blacktriangle$), B_{max} = 2.35, K_D = 191.24.

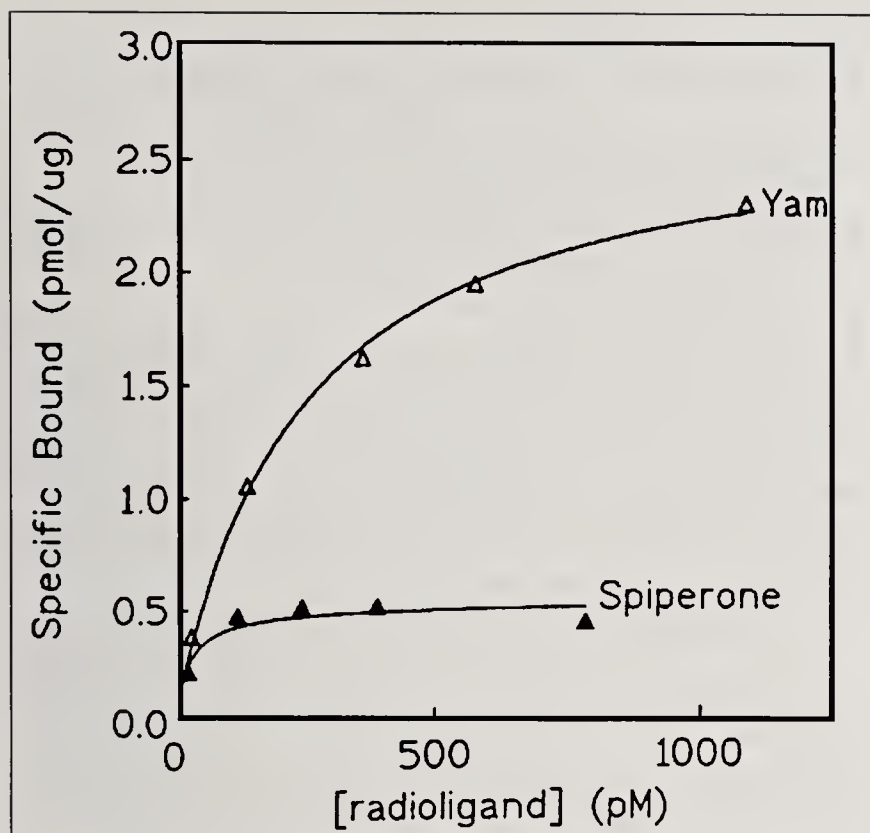


Figure 4. Radioligand binding assay of membranes from Sf9 cells expressing the D2 receptor using [^3H]-YM-09151-2. The membranes were treated with dopamine, okadaic acid or both and were from the same membrane preparation. Specific radioligand binding was defined as binding inhibited by 1 μM (+)-butaclamol. The B_{max} (pmol/mg of protein) and K_D (pM) values are as follows: Basal (■), $B_{\text{max}} = 2.27$, $K_D = 121.80$; Dopamine (▲), $B_{\text{max}} = 3.57$, $K_D = 185.96$; Okadaic acid (◆), $B_{\text{max}} = 2.13$, $K_D = 180.07$; Dopamine and Okadaic acid (●), $B_{\text{max}} = 3.83$, $K_D = 232.23$.

intensity of the monomer and dimer bands in the EDAC and drug-treated membranes were not significantly different from the membranes treated with EDAC only; the slight difference is largely attributed to inconsistent loading of amounts of membranes into each well of the agarose gel. This suggests three possible postulations: first, EDAC treatment somehow leads to the degradation of monomers, but leaves the dimers intact; second, EDAC treatment induces dimerization into a dysfunctional dimer, unresponsive to drugs, and alters the dimer in such a way that it is no longer recognized by the antibodies or third, EDAC treatment results in the formation of a functional dimer, but similarly, we cannot detect the dimer. Our laboratory has also found that photolabelling experiments on EDAC-induced dimers failed to bind any photolabel whereas the monomer was able to bind photolabel in the same membrane preparation. This finding suggests that EDAC may interfere with the ligand binding process. Thus, the possibility of an EDAC-induced functional dimer seems rather remote. Instead, the first two hypotheses are more consistent with these findings.

In the absence of EDAC, exposure to D2 agonists causes an increase in both D2 monomer and dimer numbers on the cell surface in whole-cell studies²⁵. Upon agonist

treatment, intracellular D2 receptors migrate to the cell surface; thus, the D2 receptor density increases. It has also been shown by previous investigators that antagonists also cause an increase in the D2 receptor density of both species on the plasma membrane²⁵. Likewise, intracellular D2 receptors translocate to the plasma membrane upon antagonist exposure. Hence, if we were to perform this experiment on a whole-cell preparation, both D2 monomer and dimer numbers would be expected to increase on the cell surface.

Autophosphorylation of D2 Receptors Upon Dimerization

The amino acid sequence analysis indicates that the D2 receptor contains serine and threonine residues in the third putative intracellular cytoplasmic loop, consensus sequences targeted by phosphorylating enzymes². In the PDGF receptor, ligand binding causes dimerization of receptors, which is followed by autophosphorylation²². To examine the role of phosphorylation in D2 receptor dimerization, we treated the membranes with or without dopamine and with or without EDAC in the presence of [γ - ^{32}P] ATP. Under basal conditions, an intense dimer band is present; a monomer band was not observed (Fig. 2). Therefore dimers show an increased propensity to be phosphorylated. This is consistent with previous findings that the D2 receptor is phosphorylated in the basal state¹². In the dopamine-treated membranes without EDAC, only the dimer bands were distinguishable. Unfortunately, the dimer bands in the control were of different intensities. Their difference was due to the uneven loading of phosphorylated membranes into each well of the agarose gel. Thus, we are not able to conclude for certain that dopamine exposure promotes or inhibits phosphorylation. In the D1 receptor, dopamine treatment caused a reduction in D1 receptor-stimulated adenylyl cyclase activity and an increase in phosphorylation of the D1 receptor²⁴. Thus, other studies concluded that the increase in phosphorylation of the D1 receptor may be involved in the agonist-induced desensitization of the D1 receptor-stimulated adenylyl cyclase²⁴. To extrapolate the characteristics of the D1 receptor to the D2 receptor, we would speculate that phosphorylation may also be involved in the desensitization process of the D2 receptor-inhibited adenylyl cyclase. Future experiments would be necessary, however, to uncover the role of phosphorylation in the D2 receptor.

In the EDAC-treated membranes, no phosphorylated dimer or monomer bands were present (Figure 2). Thus, EDAC seems to inhibit the phosphorylation of both species. This result seems unusual since our previous findings in this study suggests that EDAC affects either the monomer or dimer, not both. It appears, however,

that EDAC changes the D2 receptor into a dysfunctional receptor so that phosphorylation does not occur.

Pharmacological Characterization of the D2 Receptor with Two Different Antagonists

Using radioligand binding analysis, the radioligand [^3H]-YM-09151-2 has been reported to detect a two-fold or greater receptor density than [^3H]-spiperone in the same membrane preparations from rat and porcine anterior pituitary tissue and postmortem human caudate tissue^{14, 15, 16}. The differential binding of YM-09151-2 and spiperone has been interpreted that YM-09151-2 binds to both monomers and dimers whereas spiperone binds to dimers¹⁶. This hypothesis, however, was untested until now. Using photolabelling, we found the opposite (data not shown). YM-09151-2 seems to bind preferentially to dimers whereas spiperone binds to monomers only. Although these are preliminary findings, the ramifications are enormous. Because of their binding discrimination, both radioligands could be used as an analytical tool to quantify monomer and dimer receptor numbers under a myriad of conditions. From there, we could elucidate the functional significance of the D2 monomer and dimer.

Effects of Okadaic Acid on the D2 Receptor

In the PDGF receptor, dimerization of the receptor is followed by autophosphorylation,²² and we have shown that both D2 receptor species are intrinsically phosphorylated. So we treated the receptors with okadaic acid, a phosphatase inhibitor. We chose okadaic acid because it is a non-specific phosphatase inhibitor. Okadaic acid should inhibit phosphatases from dephosphorylating the receptors and therefore it should stabilize phosphorylated receptors.

Employing the differential binding characteristics of YM-09151-2 and spiperone, the total number of receptors as either dimers and monomers can be detected. In preliminary findings, the radioligand [^3H]-YM-09151-2 detected a D2 receptor density in okadaic acid-treated cells that was not significantly different from okadaic acid-untreated cells, in the presence/absence of dopamine. Therefore, as detected by [^3H]-YM-09151-2, okadaic acid does not appear to have a large effect on the binding characteristics of D2 receptors.

For the D1 receptor, it is believed that post-translational phosphorylation of the receptor induces G-protein uncoupling, resulting in a desensitized receptor²⁴.

Thus, it is possible that desensitization of the D2 receptor is also regulated by post-translational phosphorylation. The effects of other specific phosphatase inhibitors will have to be investigated, since okadaic acid failed to have a significant impact on the binding characteristics of D2 receptors.

For both okadaic acid-treated and untreated cells, dopamine exposure increased the D2 receptor density significantly, as detected by [^3H]-YM-09151-2. This is consistent with previous studies which showed that agonists mediate a slow time-dependent redistribution of D2 receptors from intracellular pools to the cell surface as assessed by radioligand binding and confirmed by immunoblot analysis²⁵. Using radioligand binding analysis, we will be continuing these studies with the radioligand [^3H]-spiperone to further clarify the role of the post-translational phosphorylation of the D2 receptor.

Summary

Immunoblot analysis revealed the presence of D2 receptor monomers and dimers. Using EDAC, a known covalent cross-linking agent, we attempted to elucidate the biochemical bonds involved in dimerization. In addition, the D2 receptors were treated with a D2 agonist or antagonist such as dopamine or spiperone. Under drug and EDAC treatment, D2 monomers and dimers did not change significantly from membranes treated with EDAC only. Phosphorylation studies revealed that EDAC-treated membranes do not undergo phosphorylation whereas EDAC-untreated membranes readily phosphorylated depending on the conditions. Together, these two findings strongly suggest that EDAC induces the formation of a dysfunctional D2 dimer that is insensitive to D2 drugs and incapable of autophosphorylation. Clearly, much more research will be needed to reveal the biochemical characteristics of the D2 dimer.

D2 receptors were treated with okadaic acid, a non-specific phosphatase inhibitor. It was hoped that okadaic acid would inhibit endogenous phosphatases from dephosphorylating the receptors and thereby stabilize the phosphorylated receptors. However, radioligand binding assays, using the differential binding characteristics of YM-09151-2 and spiperone, did not detect any significant effects from okadaic acid treatment. More studies using different phosphatase inhibitors will be needed to fully elucidate the dephosphorylation mechanism of the D2 receptor.

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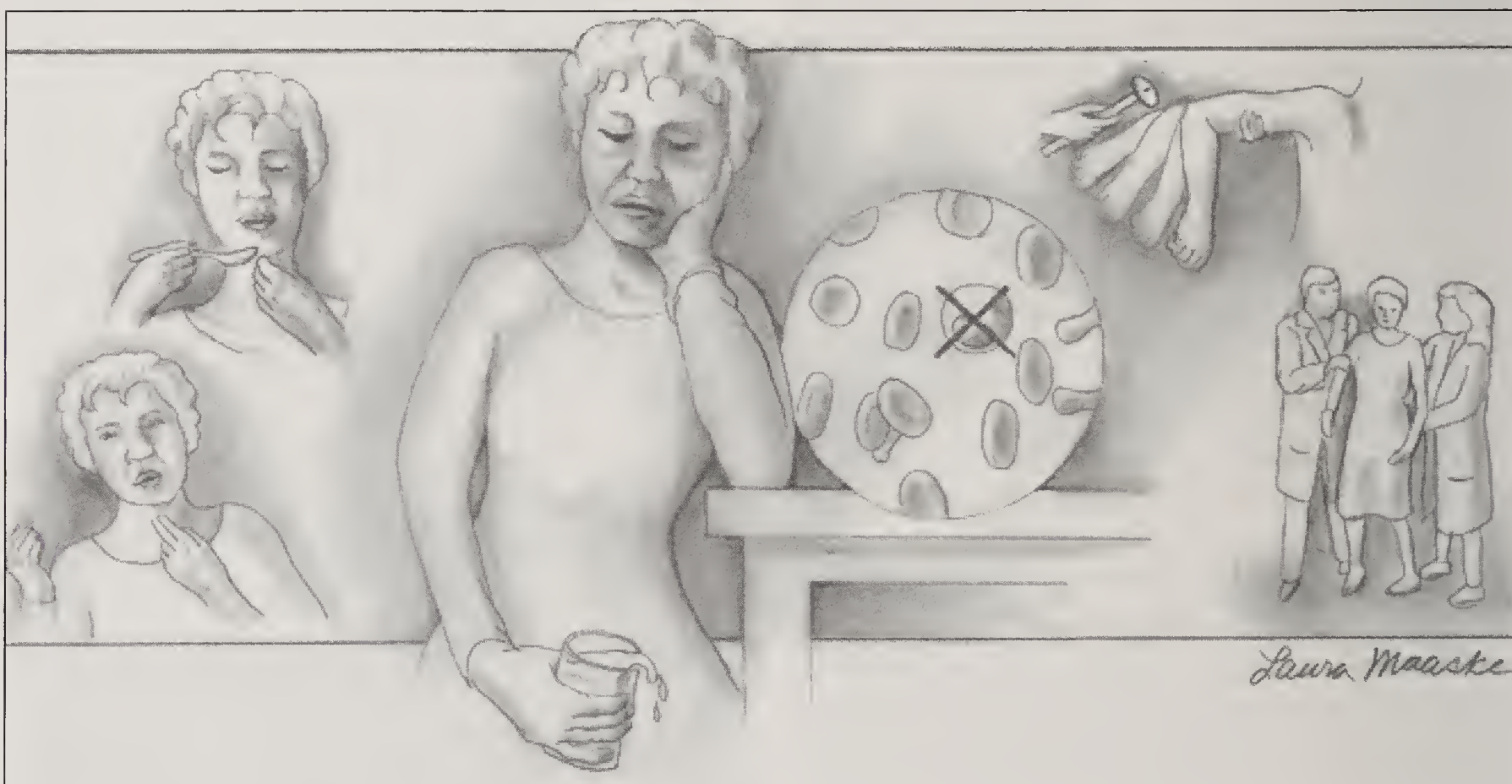
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Myasthenia Gravis and Multiple Sclerosis: Two Neurologic Disorders, One Patient

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LAURA MAASKE

Abstract

Neurology practice usually rests on the supposition that a given patient's signs, symptoms, and laboratory tests identify a single unifying diagnosis. We present a patient in whom two autoimmune neurologic disorders developed sequentially: myasthenia gravis, then multiple sclerosis. Both clinical diagnoses were supported by selective laboratory testing. This case reminds clinicians to be vigilant to the fact that autoimmune neurologic diseases, like autoimmune diseases in general, may be clustered in single patients.

Introduction

Myasthenia gravis (MG) is a disorder of the neuromuscular junction. In this prototypic autoimmune disease,

antibodies directed against the acetylcholine receptor (AChR) on the postsynaptic membrane cause an increased rate of receptor destruction. A decrease in number of available receptors leads to weakness and fatigability of skeletal muscles which fluctuates in severity. The characteristic distribution of muscle weakness typically results in complaints of double vision, difficulty swallowing and speaking, and limb weakness and fatigue. Thymic abnormalities, particularly thymic hyperplasia and thymoma, are common in these patients. Tests of response to anticholinesterase agents, electrodiagnostic studies, and measurements of serum anti-AChR antibody levels are used to confirm a suspected diagnosis. Methods of treatment include anticholinesterase medications, immunosuppressive agents, thymectomy, and plasmapheresis.

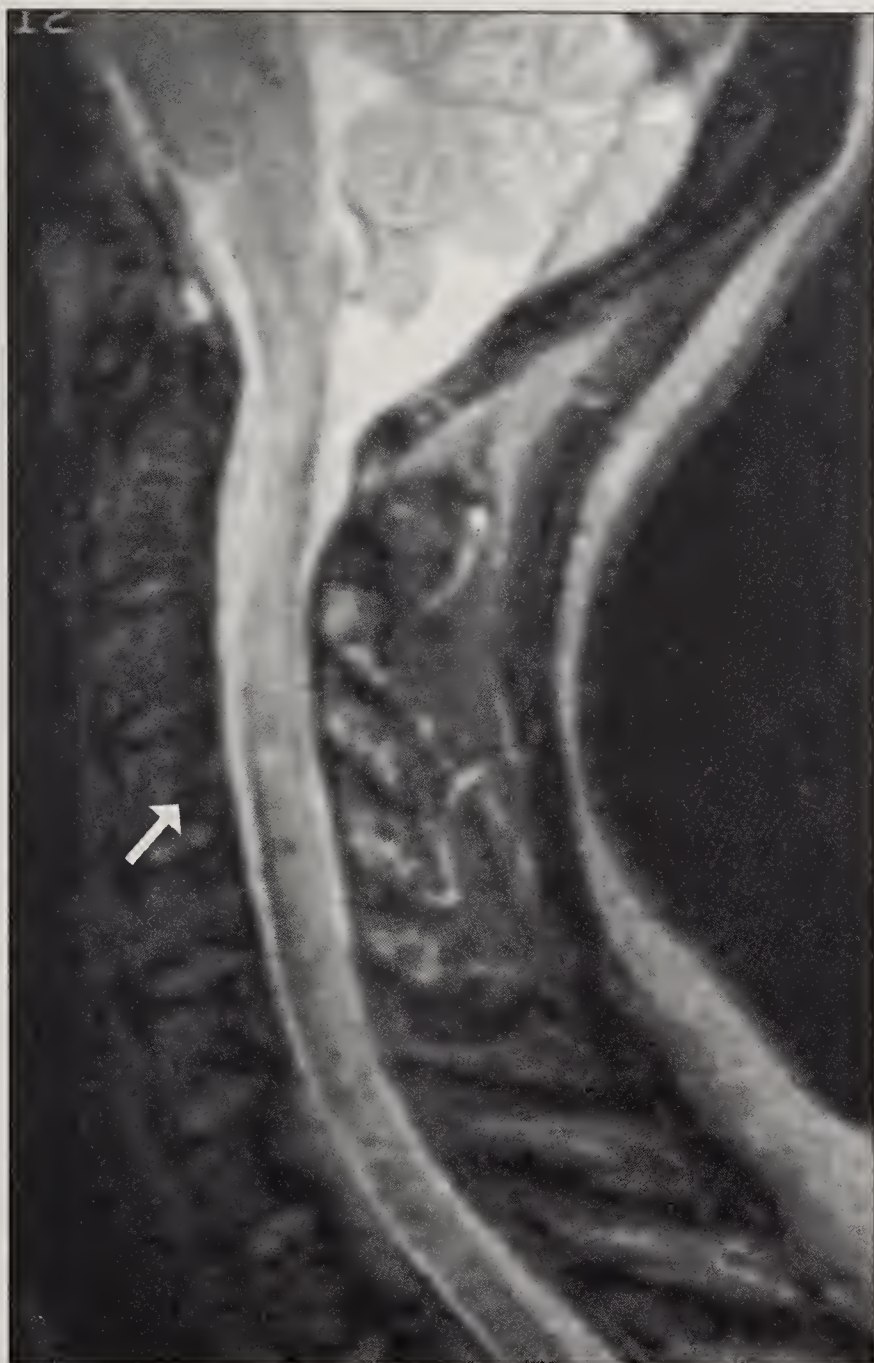


Figure 1: T2-weighted sagittal magnetic resonance imaging (MRI) of cervical spine (TR = 2069, TE = 70) reveals extensive hyperintensity and slight swelling of entire cervical spinal cord consistent with acute demyelination.

Multiple sclerosis (MS), the second neurologic condition affecting this particular patient, is characterized by multiple foci of central nervous system (CNS) demyelination. Although the cause of demyelination remains unknown, indirect evidence supports an autoimmune etiology for MS¹, perhaps triggered by a viral infection in a genetically susceptible host. Specifically, MS is associated with CNS immunoglobulin production and alteration of thymus-derived or T lymphocytes^{1,2}. The pathologic hallmark of this disease is inflammation associated with selective areas of demyelination of CNS white matter, with sparing of the axons. Clinically, neurologic findings occur over an extended length of time and involve several pathways. Patterns suggestive of MS include optic neuritis and internuclear ophthalmoplegia, or either of these conditions in association with corticospinal tract or cerebellar signs. Visualization of the degenerating plaques of myelin using magnetic resonance imaging (MRI), as in Figures 1 and 2, can be used to confirm the diagnosis.

Coexistence of myasthenia gravis and multiple sclerosis, although rare, appears to be more common than would be expected by chance alone^{3,4}. We report a patient who developed clinically definite MS 15 years after the onset of MG, while her MG was in clinical remission. Careful clinical assessment and judicious use of laboratory testing identified evidence of both disorders. In the discussion following the case presentation, we postulate that the association of these neurologic disorders may reflect shared mechanisms of immunopathogenesis.

Case Report

A 41 year old right handed woman noted right arm and left hemisensory alteration followed the next day by right sided hand clumsiness and difficulty ambulating. Two weeks prior to this she had transiently experienced tingling and weakness of the left hand. There was a 15 year history of unexplained intermittent severe burning right facial pain.

Fifteen years before this current presentation she had been diagnosed with myasthenia gravis presenting with diplopia, dysarthria, dysphagia and limb fatigability. The diagnosis was confirmed by electrophysiological tests (an electrodecremental response of 25% in the left median motor territory during 4 Hz stimulation that

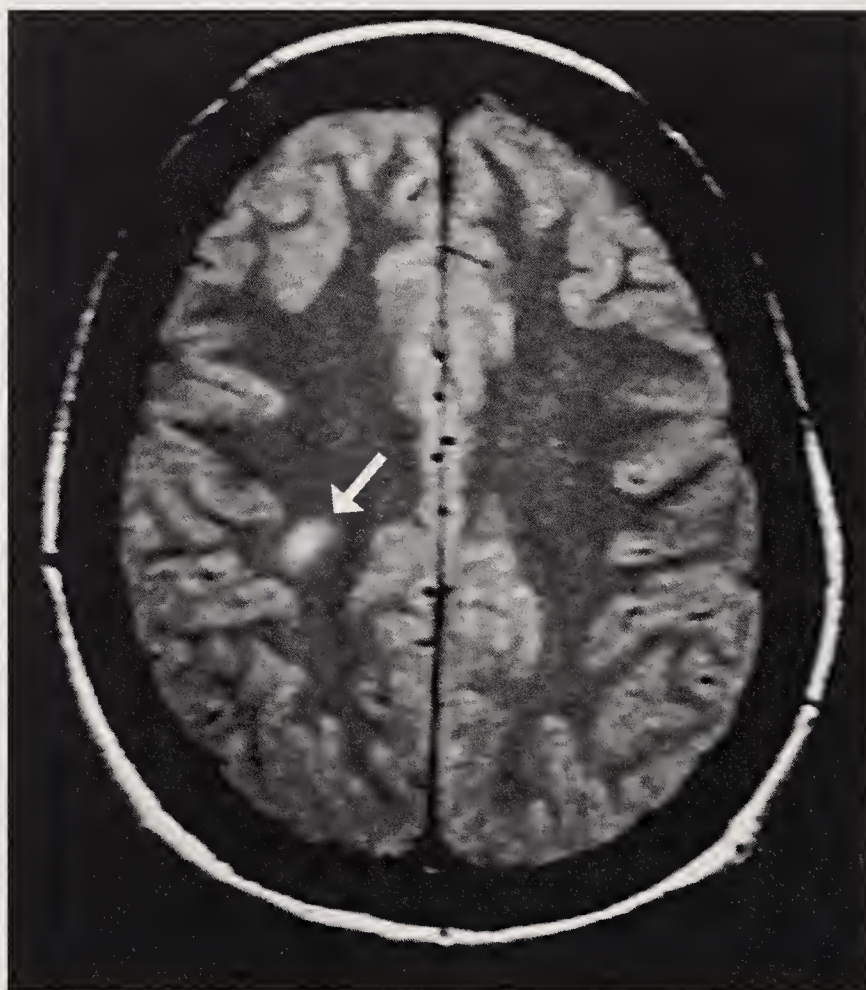


Figure 2: T2-weighted axial cranial magnetic resonance imaging (MRI) (TR = 2000, TE = 18) revealing white matter hyperintensity in right deep parietal area.

was corrected by 6 mg of intravenous edrophonium, a short-acting cholinesterase inhibitor) and by elevated levels of anti-AChR antibody in the serum. Over the next few years she was managed on pyridostigmine (a longer-acting cholinesterase inhibitor) alone, without immunosuppressives or thymectomy. Computed tomography (CT) scans of her chest did not identify a thymoma. She eventually discontinued all treatment without recurrent symptoms.

On clinical examination, there was mild weakness of the right triceps, right finger extensors, right iliopsoas, right quadriceps, and left triceps. In both upper limbs she demonstrated mild finger-nose dysmetria and deep tendon reflexes were brisker in the left upper limb than the right. Her gait was very unsteady, requiring two assistants. No other neurologic deficits were noted. In particular, there was no evidence of myasthenia gravis and she denied symptoms of it. She was admitted to hospital and spontaneously improved over the next few days.

An MRI scan provided paraclinical evidence for the presence of other lesions noted in deep right parietal white matter (Figure 1), left deep white matter and within the cervical spinal cord (Figure 2). In the cord, there was diffuse edema and multiple long linear hyperintense lesions, some extending the length of the cervical spine (Figure 2). Cerebrospinal fluid (CSF) protein and glucose were normal and oligoclonal bands were absent. There were 12×10^6 white blood cells per litre and no red blood cells. Visual, auditory, and somatosensory evoked potentials were normal. Serum anti-AChR antibody titre was elevated.

Two months following her initial presentation, she reported marked improvement. She continued to experience left hand numbness and brief episodes of limb and tongue numbness. Neurologic examination identified upper limb reflex asymmetry, and mild left upper limb ataxia only. There were no findings of MG, indicating clinical remission despite the persistence of elevated anti-AChR antibodies in her serum.

Discussion

Our case reminds clinicians that patients of any age may suffer from more than one neurologic disorder, even if they are uncommon ones. It is interesting to note that this patient had clinical remission of MG, despite elevated anti-AChR antibodies in serum, while developing an apparently new autoimmune neurologic disorder. The history, neurologic findings and MRI results rendered the diagnosis as clinically probable, laboratory

supported multiple sclerosis. The prior history, however, of atypical facial pain and transient arm tingling likely indicated that MS was present before our studies.

Clustering of autoimmune disease has been clearly demonstrated in patients with MG, where the cumulative prevalence of such diseases approximates 11%³. Despite the failure of autoimmune disease in general to cluster with MS, there is a strong suggestion that the rare association with MG may in fact be significant. Upon reviewing the literature, Lo and Feasby⁴ reported that the association of these two diseases was probably greater than the incidence that would have occurred by chance³. An epidemiological survey in Finland came to the same conclusion⁵.

The development of myasthenia gravis and multiple sclerosis in the same patient may be postulated to be due to shared pathogenic mechanisms. It is probable that the similarities between MG and MS lie in impairment of the normal immunoregulatory mechanisms that prevent the activation of self reactive lymphocytes which recognize the ACh receptor in MG, and myelin proteins in MS⁶. In normal individuals, T cell clones are present which recognize CNS myelin proteins – specifically, myelin basic protein (MBP), myelin proteolipid protein (PLP), myelin oligodendrite glycoprotein (MOG), and myelin-associated glycoprotein (MAG) -- in addition to acetylcholine receptor. Their presence is indicative of the fact that these T cell autoreactivities constitute a part of a naturally occurring T cell repertoire^{1,2}. Although it is not clear what immunoregulatory alterations may allow for the activation of self-reactive T cells, it is not unreasonable to assume that the regulatory mechanisms that prevent autoreactivity to one antigen are controlled in a similar fashion to others.

If so, common cytokine mediators of T cell activation and the presence of T-helper type 1 (Th1) and T-helper type 2 (Th2) subset commitment in one autoimmune disease may potentially allow for the nondiscriminatory activation of T cells targeting other autoantigens in another autoimmune disease⁷. Activation of autoreactive T cells may potentially result from a superantigen effect and this may well be a triggering factor in the development of these two diseases⁸. As has been proposed, the thymus is the organ where the initial AChR sensitization takes place in myasthenia gravis. This organ is frequently either atrophic or neoplastic in MG. Whether the observed changes in the thymus have implications for the process of T cell education and selection which might help explain the development of both diseases in the same patient is not clear⁹.

Unfortunately, an improved understanding of fundamental immunoregulatory mechanisms is necessary before we are likely to resolve the mechanism for the co-occurrence of these two disorders.

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Leprosy Today

Royce S.J. Ng

Abstract

Many people around the world have devoted their lives to the study of leprosy (Hansen's Disease). Recent advances in treatment using Multiple Drug Therapy (MDT) have been fairly successful in arresting many of the disease's symptoms, however, whether or not this can qualify the disease as currently having a cure is debatable. The long-term effects of untreated leprosy include specific forms of physical disability. At present, international efforts are geared toward elucidation of the disease process, development of options for treatment and rehabilitation, and ultimately, complete eradication of the disease. Research for this article was conducted at the Richardson Leprosy Hospital in the town of Miraj in Maharashtra, India in the summer of 1995. The article provides a general introduction to the disease and discusses some of the challenges faced in leprosy work in India and around the world.

A Common Place for Leprosy

When I took my first taxi-ride through the streets of Bombay, India in the summer of 1995, I felt a sense of awe. That night I saw literally thousands of people sleeping on the streets in squalor and poverty. My taxi accelerated and raced around pedestrians, bullock-drawn carts carrying their loads, heavy carrier lorries, and little children playing on the road. The constant honking of the traffic, the terrible exhaust from the combustion vehicles, and the unending business made my first experience in India quite unforgettable. In the darkness and 39°C heat of a typical summer night in Bombay, the city known as India's equivalent to Hollywood, I felt overwhelmed. I remember seeing one family with 4 children sleeping by the road-side. One of the children appeared to be little more than a month old and was peacefully asleep on a sheet of newspaper between his parents. My host with me at the time turned to me and said with a smile: "This...is India."

Although leprosy is a disease which is found predominantly in the developing world, cases exist even in

Canada as a consequence of the ease of modern transmigration. As a visitor and volunteer who wanted to learn about work being done in leprosy in a developing country, I headed to a small hospital called The Richardson Leprosy Hospital in Miraj, India. The hospital belongs to an international charity organization called The Leprosy Mission (TLM), founded in 1874, which is dedicated to meeting the needs of leprosy sufferers around the world and to one day eradicating this dreaded disease. It is involved in numerous areas of work and research, often in partnership with the World Health Organization (WHO), local governments, and other charities around the world. TLM has leprosy centers in over 30 developing countries.

Classification of Leprosy

Leprosy is also known as Hansen's disease. It is caused by the *Mycobacterium leprae* bacilli, a close relative of that which causes tuberculosis.

Different degrees of infection are categorized under what is known as the LL-TT spectrum. At one extreme is lep-



Figure 1: A young girl's first sign of leprosy - a hypopigmented patch.

ramatous leprosy (LL) which is most severe and at the other is tuberculoid leprosy (TT) which is least severe. The mid-way point in the spectrum is known as borderline leprosy (BB).

Transmission of Leprosy

Although there is debate as to exactly how leprosy is transmitted, it is widely held that airborne bacilli from infected and untreated patients' nasal secretions are responsible. Contrary to common belief, the disease is not highly contagious and its progression is in fact very slow, i.e.-in months and years instead of days or weeks. In the lab, the bacilli can be seen under light microscope in skin smears or nasal secretions by using a similar acid-fast staining technique to that which is used for detecting the tuberculosis bacilli.

Prolonged exposure to the airborne bacilli and poor resistance to *M. leprae* have been cited as risk factors for infection. Because disease progression is very slow and its transmission is somewhat random, it has been difficult to determine the exact mode of transmission. For example, a couple suffering from leprosy may have a child who grows up never having contracted the disease. Many doctors, nurses and paramedical workers have worked for decades amidst leprosy, having close daily contact with infected patients and never develop symptoms of infection themselves. In some areas that have been completely treated and 'cured' of leprosy, new cases arise, thereby making it very difficult to determine exactly how and when the victims were infected.

Symptoms and Long-Term Effects

The disease manifests itself in skin and in specific areas of the nervous system. Early symptoms include patches of hypopigmented skin, specific nerve inflammation (neuritis), specific muscle weakness or paralysis, and anaesthesia of skin and body parts. Leprosy is a disease that afflicts both young and old. Figure 1 shows a girl being tested for skin anaesthesia. The single hypopigmented patch on her left arm was the presenting symptom of her leprosy.

Figure 2 shows a youth with partial nerve damage affecting his right hand. Partial clawing can be seen in the 3rd and 4th finger. As the disease progresses, disabilities set in such as claw-hand, foot-drop, blindness, nasal depression and bone and tissue damage due to osteoporosis. Late stages of untreated leprosy are seen in Figure 3. The patient is an adult male with severe and complete clawing in both hands and foot-drop in both feet. As voluntary dorsal foot flexion is not possible due to nerve damage, a set of straps are worn to prevent further injury to his feet from walking.



Figure 2: Partial clawing in the 3rd and 4th finger of the right hand compared to the normal left hand.



Figure 3: Severe and complete clawing in both hands and foot drop can be seen in this adult male. Specially made straps are worn to keep the feet from dragging while walking.

Further complications such as infections, severe ulcerations and sepsis will occur to repeatedly traumatized body parts as a consequence of the localized anaesthesia. Quite often, such repetitive trauma could occur during routine daily functions as simple as squatting or walking or from occupational activities. For example, a heavy smoker might sustain repeated burns to his or her fingertips due to anaesthesia in the hand. Another example is a person with a fold or crease in their shoe that is not noticed due to the anaesthesia in the foot. These both will eventually lead to blistering, ulceration, infection and then disability.

Treatment

There is a reliable treatment for leprosy. In the 1980's an oral drug regimen known as Multiple Drug Therapy (MDT) was introduced which primarily includes dapsone, rifampin and clofazamine. The exact regimens will depend on the stage of the infection, as indicated by the LL-TT spectrum, and may last between 6 months to 2 years or indefinitely. MDT is able to prevent the progression of the leprosy bacilli, thus rendering the patient non-infectious. MDT is not devoid of side-effects (known as 'reaction') and does not always prevent the development of relapse symptoms. To treat the side-effects, adjuvant therapy in the form of steroids may be administered.

Possibilities of Eradication

One main objective of the World Health Organization and TLM is of course to eradicate leprosy altogether. However, during my visit to India, I witnessed individuals with new cases of leprosy literally walking off the street and into the mission hospital. Children with single lesions and cases of lepromatous type children, both having never received any treatment were found. I also had the chance to go on some surveys with leprosy control teams to search for new cases of leprosy in remote villages and communities. During their diligent door-to-door work, tedious head counts and on-the-spot examinations for leprosy were made to proactively locate and treat new leprosy cases. As well, the leprosy workers spent time educating communities about how to identify leprosy and about the steps to take when leprosy is suspected.

Currently, much work is being done to produce a vaccine against leprosy. Unfortunately, in places such as India, even diseases that already have vaccines are still potent killers since administering proper vaccinations in developing countries is an enormous task.

Significant difficulties arise due to patient non-compliance with therapy, unavailability and cost of medication and education, and the logistics of detecting new cases before they develop and spread to others. Eradicating a disease such as leprosy requires a fundamental increase in the standards of health, education and welfare of the population affected. Today, leprosy remains a disease of the impoverished.

One Little Leprosy Hospital

I learned much about leprosy during my 6 week stay at The Richardson Leprosy Hospital in the town of Miraj in Maharashtra, India. The hospital, headed by Dr. Vijay-Kumar Edward, has approximately 125 beds. The center possesses humble yet relatively comprehensive facilities for leprosy work.. The hospital has male and female patient wards and ulcer wards, an outpatient clinic, a physiotherapy room, a pharmacy, a cytology/microbiology lab, operating rooms, x-ray equipment, and an immunology research laboratory. The hospital also has a facility for making orthopaedic shoes, a prosthetics room, and a weaving center which teaches patients how to make handbags and other items which are sold to supplement their income. With 4 doctors, 2 physiotherapists, 1 social worker, 1 medical records officer, several paramedical workers and nurses, 2 lab technicians, 1 pharmacist, a post-doctoral immunologist and his lab staff, 2 pastors, and a team of administrative staff, comprehensive care is provided for hundreds of leprosy patients.

The approach to leprosy at the hospital is multifaceted. The staff realize that treating patients with drugs is not sufficient. Many patients need job-skills training and vocational guidance after their treatment is completed. Leprosy is infamous for its ability to destroy families and confine its sufferers to lives of isolation and ridicule.

With compassion for leprosy patients around the world, leprologists and scientists continue in their diligent attempts to conquer this dreaded disease and look forward to the day that leprosy will be eradicated forever.

Acknowledgments

Special thanks to staff of TLM Canada, Dr. V.K. Edward and Dr. Mark Wise.



Bank of Montreal

Obstetrics and Gynaecology Rounds

Danyal Ibrahim, M.Sc. (9T7)

The winner of the UTMJ Quick Diagnosis Competition, Surgery Rounds (Vol. 73, No.1, December 1995) is Hari Mallidi (9T7). The Journal will be offering a prize of **\$50** to the reader who submits the correct diagnoses for all the cases. Responses should be sent to the following address no later than **March 30, 1996**.

Quick Diagnosis Competition

c/o Danyal Ibrahim - Quick Diagnosis Editor

University of Toronto Medical Journal, Room 2141, Medical Sciences Building, Toronto, Ontario M5S 1A8

Email: danyal.ibrahim@utoronto.ca

Case 1 *Nicholas Leyland, B.A.Sc, M.D., F.R.C.S.(C)*

Clinical History

A 25 year old woman presents at 32 weeks gestation with vaginal bleeding. An ultrasound is ordered after an initial assessment and stabilization.

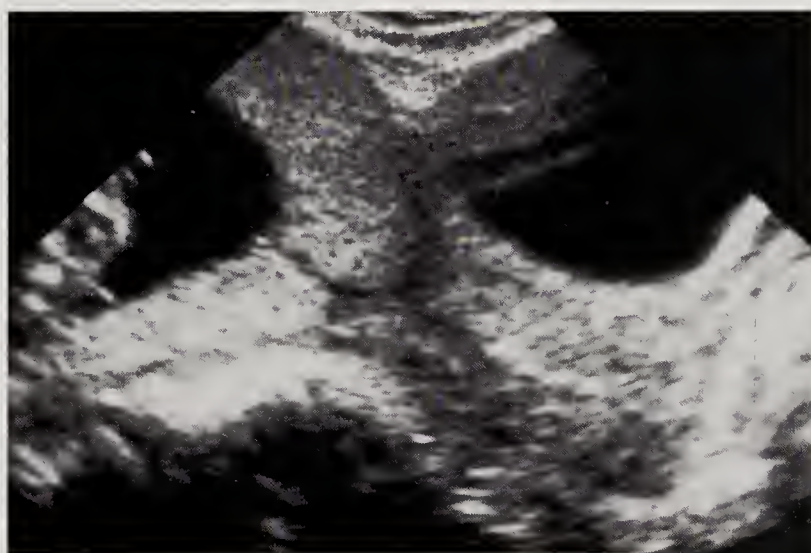


Figure 1: Image of an obstetrical ultrasound showing the abnormality.

What is the most likely diagnosis?

Dr. Leyland is an Assistant Professor of OB/GYN, Head, Division of General OB/GYN, The Toronto Hospital.

Case 2

Nicholas Leyland, B.A.Sc, M.D., F.R.C.S.(C)

Clinical History

A twenty year old woman presents with a two day history of vaginal bleeding. Her last menstrual period was twelve weeks ago. As part of the workup this ultrasound was ordered.

What is the most likely diagnosis?

What blood test could be useful?

What is the initial treatment?

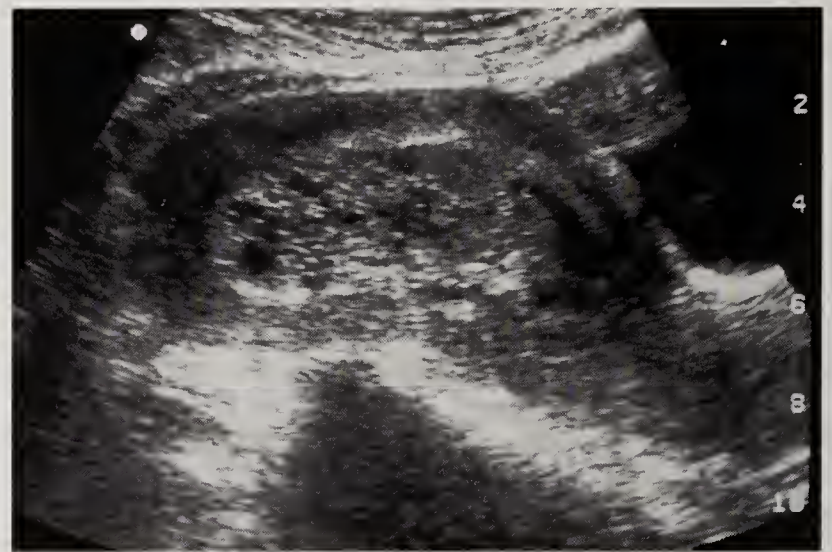


Figure 1: Image of a pelvic ultrasound showing the abnormality.

Dr. Leyland is an Assistant Professor of OB/GYN, Head, Division of General OB/GYN, The Toronto Hospital.

Case 3

Nicholas Leyland, B.A.Sc, M.D., F.R.C.S.(C)

Clinical History

A twenty eight year old woman is complaining of pelvic pain during menstruation and of dyspareunia. At laparoscopy the following findings are noted.

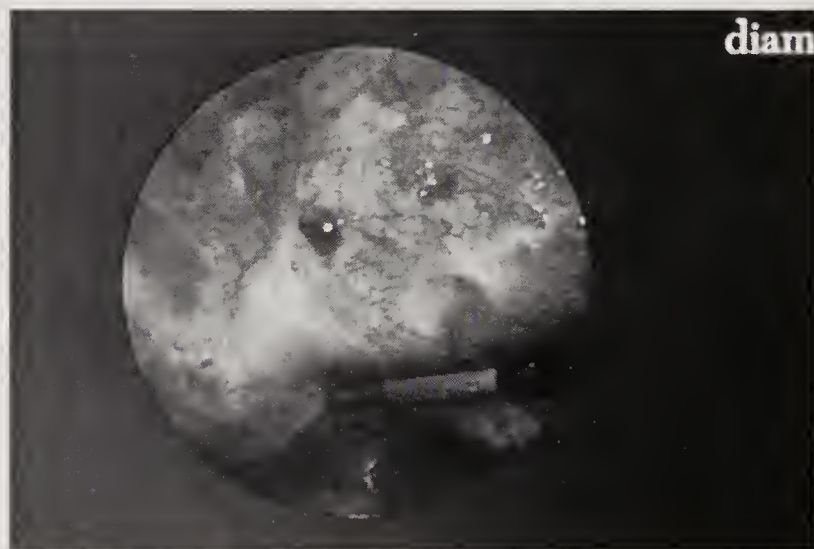


Figure 1: Laparoscopic image showing a pigmented lesion in the Cul-de-sac.

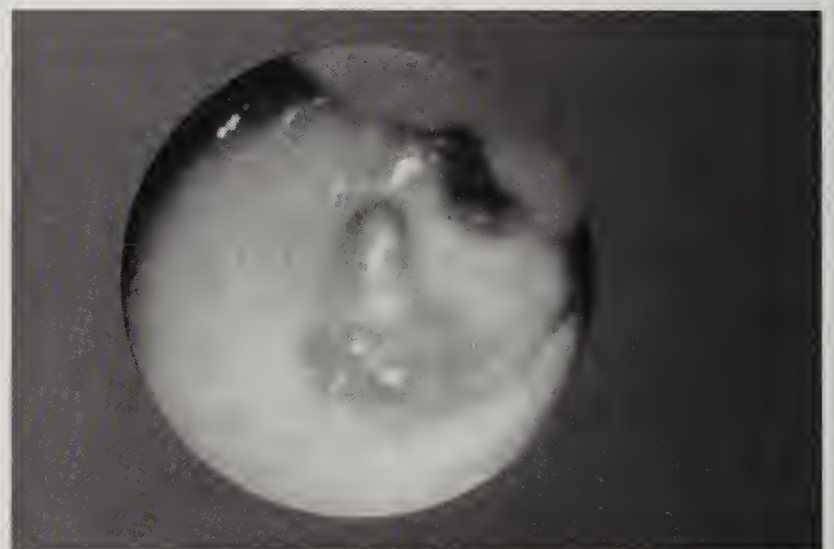


Figure 2: Laparoscopic image showing another pigmented lesion on the ovary.

What is the most likely diagnosis?

Dr. Leyland is an Assistant Professor of OB/GYN, Head, Division of General OB/GYN, The Toronto Hospital.

Case 4

Howard Cohen, M.D., F.R.C.S.(C)

Clinical History

A 25 year old G2 P1 with unremarkable medical history presents at 16 week gestation with an abnormal triple screen showing a high alpha-fetoprotein. The patient was referred for level II ultrasound.

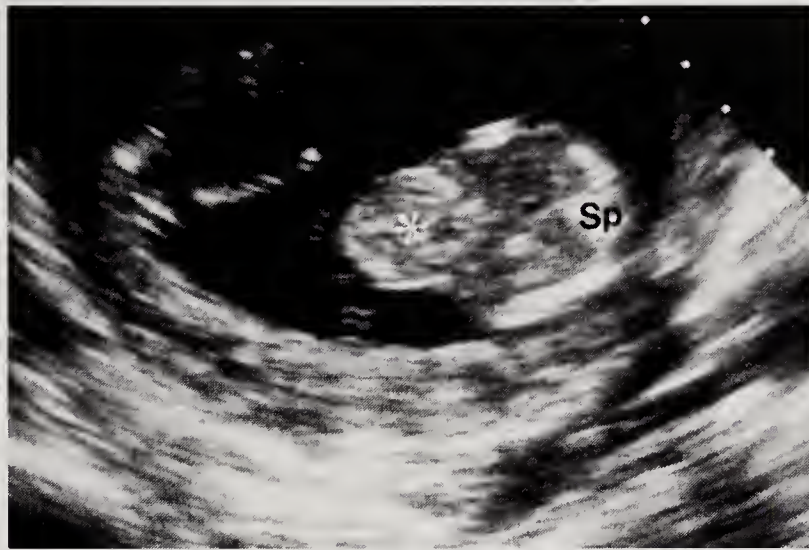


Figure 1: Ultrasound image showing transverse scan of the abdomen at the level of the umbilicus demonstrating the lesion.



Figure 2: Typical midline lesion in the newborn.

What is the most likely diagnosis?

Dr. Cohen is a Staff Obstetrician, Division of OB/GYN, The Women's College Hospital.

Case 5

Rose Kung, M.D., F.R.C.S.(C), M.Sc

Clinical History

A 60 year old G3 P3 presents to your office complaining of suprapubic pressure and a mass protruding from the vagina. She also had noticed increasing difficulty with defecation and urination as a result of the mass. In order to empty properly, she is often required to reduce the mass vaginally with her finger. The mass seems to be slowly increasing in size over the last 2 years and is worse at the end of the day. She works in a factory in the packaging section and needs to lift heavy boxes on a daily basis. She is a nonsmoker and drinks alcohol occasionally. She has had no previous surgery and has no underlying medical illnesses. She has regular pap smears. Her menopause was at age 50. She is not on any medications. On examination, she has a significant cystocele and rectocele.

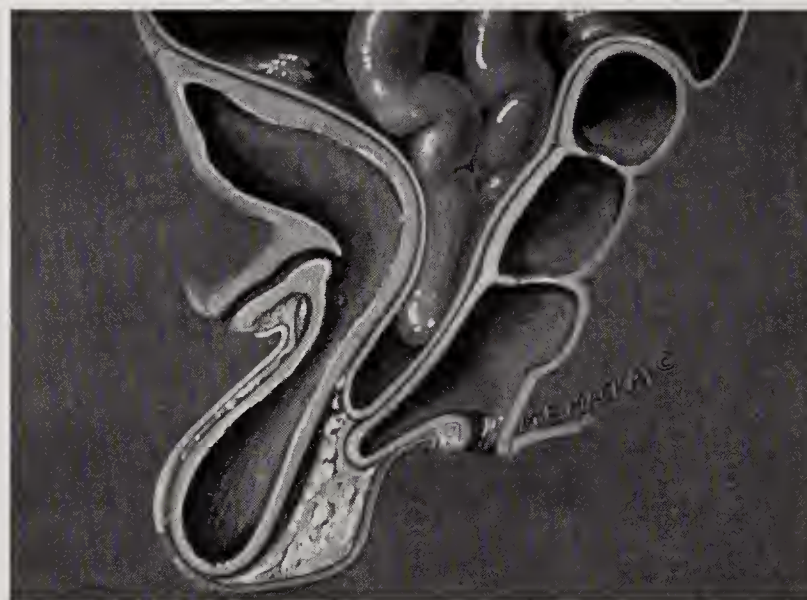


Figure 1: Illustration of a massive prolapse of bladder and bowel.

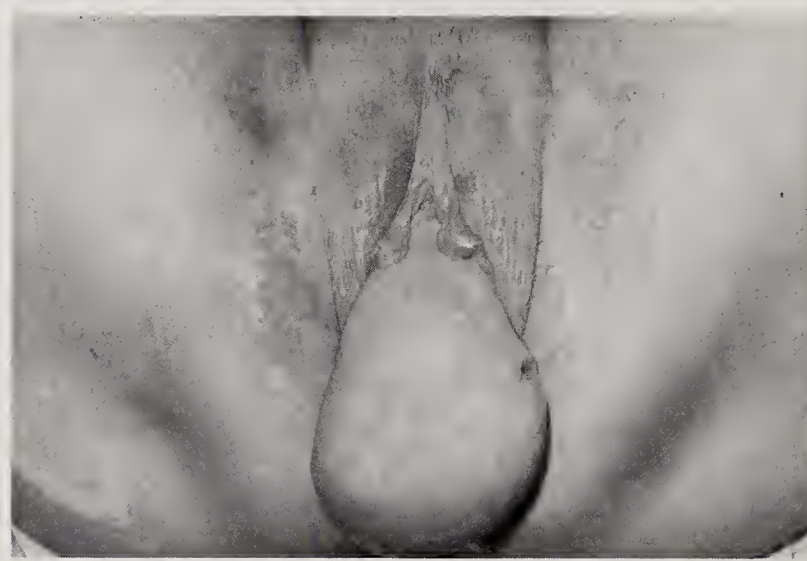


Figure 2: A photograph showing a massive vault prolapse.

What further investigations would be helpful?

What treatment options would you discuss with her?

Dr. Kung is a Staff Obstetrician and Gynaecologist, Division of OB/GYN, The Women's College Hospital.

Case 6

Rose Kung, M.D., F.R.C.S.(C), M.Sc

Clinical History

A 45 year old G2 P2 presents with leakage of urine with coughing and exercise. This has been slowly getting worse for the past 3 years and now she has to wear a pad all of the time. She denies any urgency, nocturia, and enuresis. She has gained about 15 lbs over the past 3 years. She has not had any surgery. She is not taking any medications. On examination, the uterus and adnexa are normal. She leaks urine when coughing with a full bladder.



Figure 1: Cystourethrogram (R)



Figure 2: Cystourethrogram (S)

What is the most likely Diagnosis?

What are your recommendations with respect to treatment?

Dr. Kung is a Staff Obstetrician and Gynaecologist, Division of OB/GYN, The Women's College Hospital.

ANSWERS TO QUICK DIAGNOSIS: (UTMJ Volume 73, Number 1, December 1995) Surgery Rounds

Case 1

Diagnosis: **Lymphoma**. The trismus and otalgia are due to tumour invasion of foramen ovale (involvement of trigeminal nerve) and pterygoid muscles.

Case 2

Diagnosis: **Acute Polyethylene Fracture in an Uncemented Acetabular Cup**

Case 3

Diagnosis: **Traumatic diaphragmatic hernia (chronic)**

Case 4

Diagnosis: **Ventricular septal defect following myocardial infarction**

Case 5

Diagnosis: **Ischemic mitral regurgitation +/- left ventricular dysfunction**

Case 6

Diagnosis: **Avascular necrosis of the femoral head (early onset osteoarthritis)**



Operating on the Frontier: Memoirs of a Pioneer Canadian Neurosurgeon

Frank Turnbull

Capilano Publishing, Madeira Park, Canada 1995

1994

307 pp.

Autobiographical accounts of lives marked by fascinating undertakings and bold adventures are often published and read for the substance of the account, though the writing may leave something to be desired. The memoirs of Dr. Frank Turnbull are a happy exception to this rule. In *Operating on the Frontier: Memoirs of a Pioneer Canadian Neurosurgeon*, Dr. Turnbull recounts his early upbringing in Vancouver and the formative experiences of his adolescence. He first traces his emerging interest in medicine and later in the then embryonic field of neurosurgery. Turnbull relates his impressions and experiences as a Canadian surgeon stationed in Europe during the horrors of the Second World War and details his career as a renowned neurosurgeon at Vancouver General Hospital and Associate Professor of Neurosurgery at the University of British Columbia. Dr. Turnbull demonstrates a remarkable memory for details, often of encounters with patients from fifty years ago or more. His writing is clear and unadorned and reveals the experiences and convictions of a gifted man motivated by deep compassion and a strong sense of humanism.

Frank A. Turnbull was born in Goderich, Ontario in 1904, the grandson of a Scottish immigrant and son of a respected country doctor. Dr. James Turnbull was a member of the 1889 graduating class of the University of Toronto Medical School and bore many of the qualities with which his son Frank was later imbued, including a frugal temperament, a sincere appreciation for the difficulties of others, and a quiet skepticism. In 1907, the Turnbull family moved to Vancouver, and Frank Turnbull's accounts of his childhood experiences there provide a vivid perspective of Vancouver in the 1920's as seen through the eyes of a child. Frank Turnbull attended the University of British Columbia for four years (1919 to 1923), and worked on survey teams along the BC coast during the intervening summers. Dr. Turnbull plainly relishes anecdotes from his adolescence.

Frank Turnbull graduated with the class of 2T8 from the University of Toronto Medical School, and began an internship at Toronto General Hospital. His fascination with neurology led him to train as a neurosurgical resi-

dent at TGH under Dr. Ken McKenzie. After completing his training in Toronto, Dr. Turnbull, pursued post-graduate studies in neurosurgery in England, and later in Germany. His accounts of the early periods of his career reflect both the state of the emerging practice of neurosurgery, and the degenerating political climate in Europe during the early 1930s. Turnbull returned to Vancouver and a position as staff neurosurgeon at Vancouver General Hospital in 1933. Dr. Turnbull provides us with a clear and fascinating account of the difficulties associated with establishing a practice in a field then widely regarded as exotic and futile.

The book is rounded out by an overview of clinical challenges such as infection, paraplegia, tumours, epilepsy, and hydrocephalus, which were faced daily during the practice of neurosurgery, and an historical account of the evolution of the strategies with which these challenges are met. The order of the book loosely follows the chronological order of Dr. Turnbull's career, ending with his involvement as a statesman and virtual institution in the Canadian medical community and abroad. He out-

OPERATING on the FRONTIER

Memoirs of a Pioneer Canadian Neurosurgeon



Dr. Frank Turnbull

lines the dramatic changes to the Canadian health care system in the 1960's, detailing his involvement with the Workers' Compensation Board, and offers his thoughts on the effect of medico-legal jurisprudence on the practice of medicine in Canada. The scope of this autobiography is broad, and certain sections may prove too detailed or too specialized to be of interest to some readers. However, the book is clearly organized into Dr. Turnbull's personal history, the influences which fed his development as a neurosurgeon, his views on the evolution of the field of neurosurgery, and the state of medicine in Canada as it is currently practiced. Thus, one may easily identify and confine oneself to sections of obvious interest. Overall, the book represents a fascinating and well-written account of the significant life events of one of Canada's premiere medical personalities.

Andrew Schumacher, M.Sc., (MD.PhD, Year 3)

Environmental Medicine

Stuart Brooks, Michael Gochfeld, Jessica Herzstein, Marc Schenker, and Richard Jackson
Mosby-Year Books, 1995
780 pp.

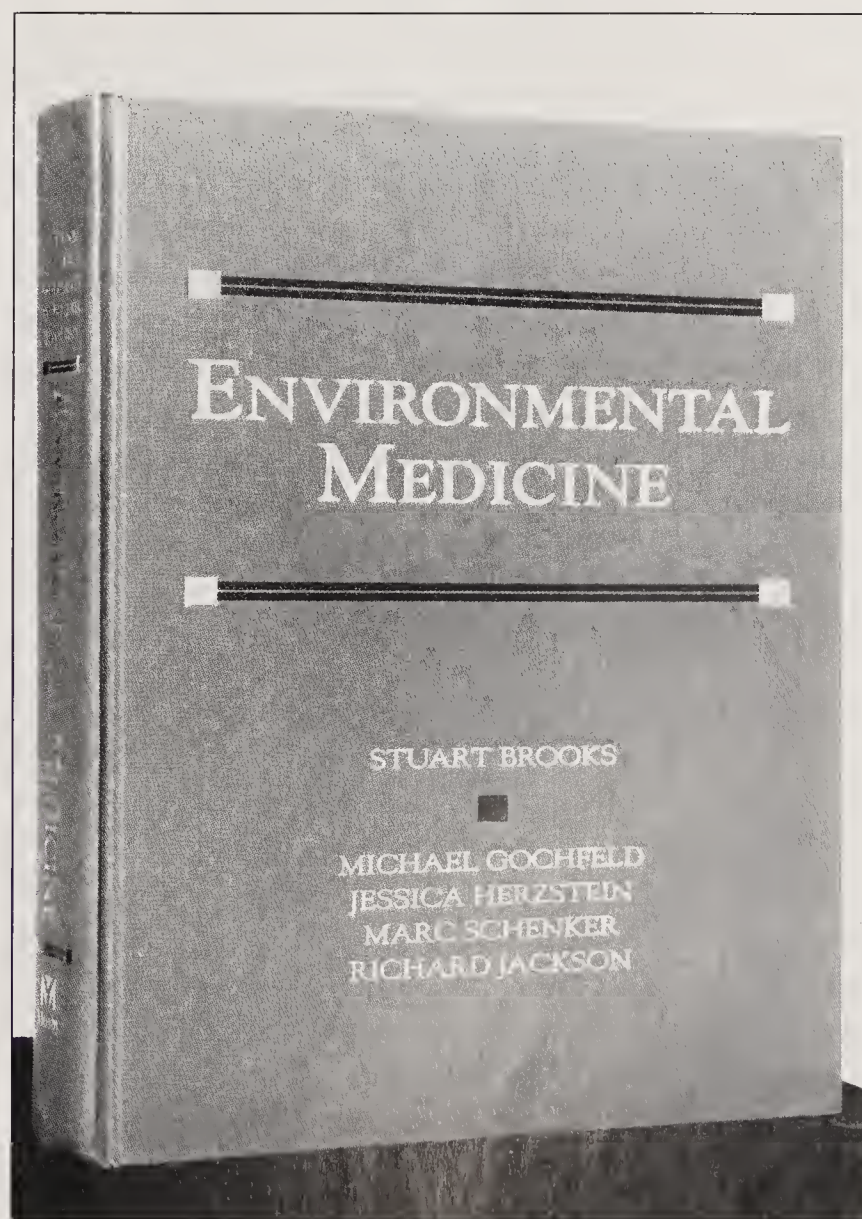
Environmental Medicine is a comprehensive textbook intended for both primary care and public health physicians who work with patients demonstrating signs and symptoms attributed to agents in their environment. As stated, a main purpose of this book is, "to furnish a comprehensive resource of scientific information on environmental health: the study of effects upon human beings of external physical, chemical and biologic factors in the general environment."

To achieve this objective, there are total of 67 chapters divided among six main parts: (1) principles in environmental medicine; (2) basic science of environmental medicine: mechanics and principles; (3) clinical environmental medicine; (4) susceptible populations and special patient groups; (5) specific environmental exposure sources; and (6) preventative approaches in environmental medicine. Each chapter has been written by a different author and concisely summarizes the available literature with complete references on particular topics. Within each chapter there are many tables, and figures used to complement the text. Overall, the chapters are arranged logically which, along with a complete index, simplifies the process of searching for a particular topic.

This book presents many important and relevant issues for physicians treating patients with environment-relat-

ed disorders. For example, the first part of the book reviews the general principles of environmental medicine. These principles include the types of environmental hazards, exposure and risk assessment, and basic epidemiological concepts. This book also discusses practical aspects such as a clinical approach to the diagnosis and treatment of environmentally related disorders of selected systems. Other issues examined include specific environmental exposures such as asbestos exposure, indoor air pollution, ionizing radiation, and hazardous wastes. On a wider population health level, this book also discusses preventative approaches in environmental medicine and current United States federal environmental legislation.

With many controversial topics in this area, the authors have done an excellent job of ensuring that each chapter remains objective. For example, multiple chemical sensitivity (MCS) is a controversial topic in which an individual demonstrates multiple symptoms in response to exposure to chemicals at levels lower than those tolerated by the general population. MCS has traditionally been a disorder dismissed by the medical community as psychological. However, the author presents all available theories: psychiatric, respiratory, immunologic and olfactory-limbic, with referred scientific evidence to support or refute each hypotheses.



One weakness of this type of textbook is that the information on hazardous substances can quickly become outdated as new substances become available and information on existing substances are released. Acknowledging this deficiency, this book has provided through its appendices a list of good sources for information such as key federal agencies, CD-ROM databases, and microcomputer databases.

In conclusion, for any physician or medical student interested in assessing and understanding the effects of the external environment on an individual's health, Environmental Medicine would be a valuable reference.

Barry Chow, (9T7)

The Complete Breast Book

1st edition

June Engel, Ph.D.

Key Porter Books

1996

288pp

\$21.95

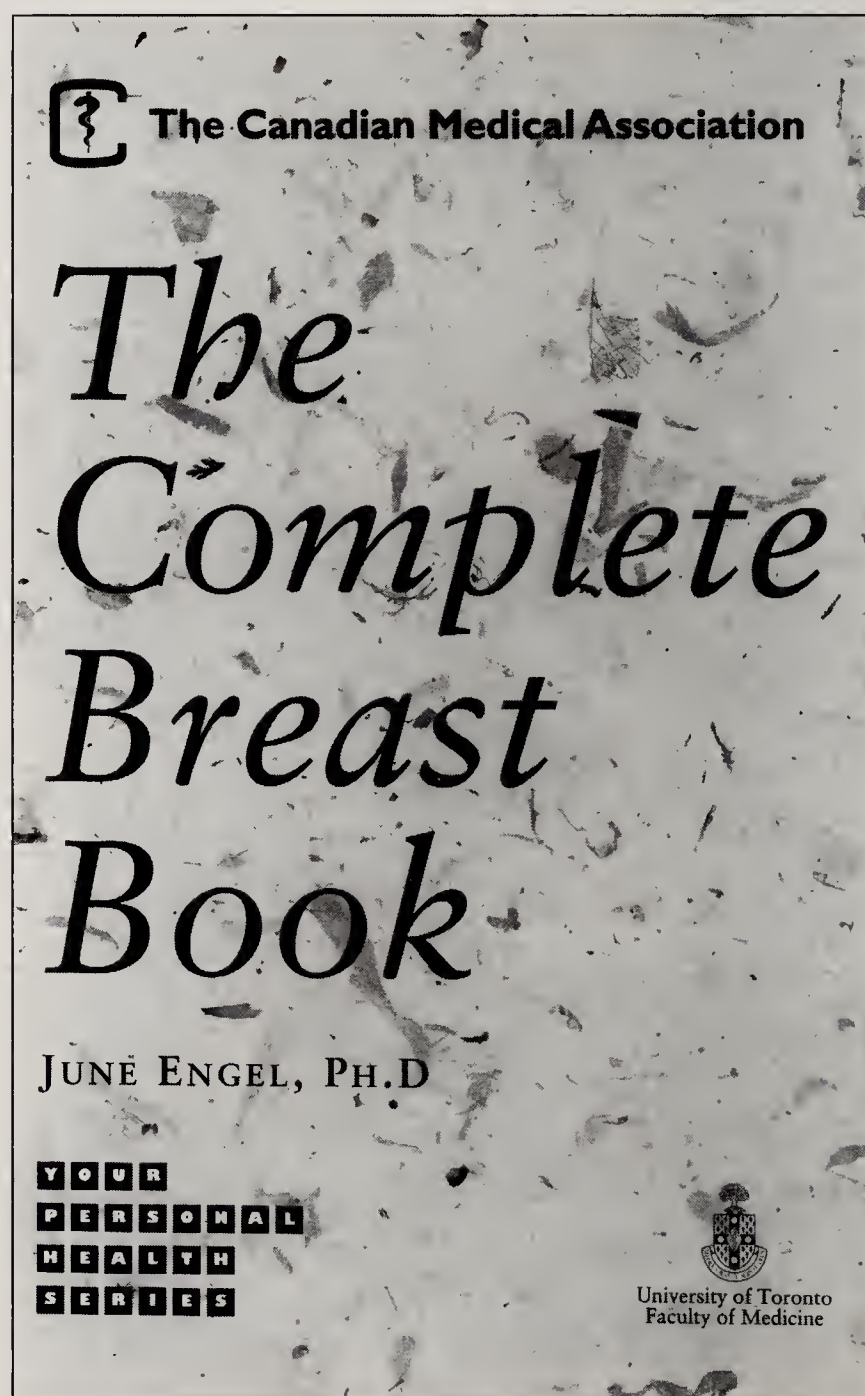
The Complete Breast Book is designed to be a woman's guide to breast disease with emphasis on breast cancer. It's focus is on dismissing the misconceptions that women have with regard to breast cancer and on providing them with current and in depth information based on medical facts. The book covers a wide variety of subjects, from breast anatomy to techniques for surgical reconstruction after mastectomy, and each chapter is designed to investigate a topic or area of interest. It is an easy to read book with adequate "translation" of clinical/medical jargon.

The book has an impressive array of chapters, all of which touch on relevant topics with regard to breast disease, from its detection to clinical investigation and treatment. While the author has chosen to cover all of the important aspects of breast disease, the chapter ordering is often confusing and frustrating. The book begins with a chapter on basic breast anatomy and proceeds through a chapter on the differential findings of benign breast lump followed later by a chapter on self breast exam (SBE) and then on suspicious lumps. This is all covered before giving a good overview of the disease

itself and importantly, of the risk factors associated with breast cancer. While these topics are covered later in the book, it seems best to arm a reader with the overall picture and an appreciation of how it relates to her specifically, before diving into the physical findings themselves.

Organization aside, many of the chapters contain solid information with up to date recommendations. In particular, the author discusses current trends in treatment with reference to the St. Gallen Consensus Conference (1995) on chemotherapy. She also reiterates the important aspects of the pathological diagnosis, the nodal status in particular, with respect to further adjuvant treatment. The breast cancer overview chapter, albeit late, is very current and obviously well researched. Each chapter also has helpful illustrations, charts and "important information" boxes which emphasise the important facts with regard to the information presented in the chapter. This would be a beneficial way to get "just the facts" in terms of quick indexing of the book.

Although the book does provide numerous facts that are substantiated by medical evidence, the phrasing of some



of the author's statements regarding certain topics that remain controversial seems to suggest that they are accepted by the medical community. For instance, in the chapter on who is at risk for breast cancer, several listed "risk factors" including alcohol, oral contraceptive use and hormone replacement therapy are still hotly debated both in the popular and scientific literature. Each of these areas warrants further investigation before any definitive statement can be made and the author needs to qualify these factors as being risks. It is also important to note that all of the risk factors for breast cancer (except for family history), are for the most part poorly understood and are based on correlational and epidemiological data rather than "cause and effect". This is critical in light of the fact that many women who do have breast cancer may not have many of these risk factors, and conversely many who have numerous risk factors may never develop the disease. In a book designed to alleviate anxiety and fear, it is important to emphasize these facts. The author also makes some clearly false statements such as "pregnancy shuts off estrogen production" in explaining the seemingly protective effect of early (before 30 years of age) pregnancy. While the biology of such protection is not understood it is not due to a shut off of estrogen production since estrogen levels are significantly elevated in pregnancy. Furthermore, in listing the side effects of tamoxifen, the author concentrates on endometrial cancer while failing to mention the risk of development of DVT. While both are rare, they are equally noteworthy.

While the book is concise in its approach, there are some places where space could be utilized to greater advantage. Noteworthy is a full page diagram in the first chapter which displays pictures of various sizes and shapes of breasts with the comment that "breasts come in all shapes and sizes." Hopefully by the time a woman would consider buying a book on breast cancer, empirical observation would have affirmed this notion in her own mind. The waste of valuable space with this needless illustration is disappointing considering that it could have been put to excellent use to display the proper hand technique used to examine a breast during SBE. Commentary on the sensual pleasures of breasts and the trite dialogue on changing fashions with regard to bras and cleavage displays really have no place in a book that is designed to provide sound medical information and "help assuage needless fears and banish misconceptions". It is a sad fact in Western culture that breasts are seen as sexual objects and are used on a regular basis to objectify women. This gross commercialization of a woman's sexuality often leads to a woman ignoring important signs of breast disease for fear of social stigmatization. Entire theses could be written on these topics and they need not be addressed in such a superficial manner. This

space could have been better used in the latter chapters to deal more completely with the emotional issues surrounding mastectomy, or an additional chapter could have explored the attitudes of women with breast cancer regarding their sexuality and breasts following treatment.

Overall, *The Complete Breast Book* was written as a guide for the layperson in order to take them through the process of breast lump detection and diagnosis. While several chapters of the book provide excellent information, it is not always easy to follow and some chapters are incomplete. I would feel confident referring breast cancer patients to certain chapters in this book (chemotherapy, radiation and surgery and reconstruction) but I would be reluctant to recommend it to women in general as a way to learn about their breasts and breast cancer.

Melinda Anne Musgrave Ph.D. (9T8)

Just bowling...



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Reprinted from UTMJ 1924; 1(3): 94-98, plus advertisements.

The University of Toronto Medical Journal

VOL. I

FEBRUARY, 1924

No. 3

THE DISCOVERY AND PREPARATION OF INSULIN

F. G. BANTING and C. H. BEST.

There have been numerous reviews of the literature which deals with attempts to prepare potent pancreatic extracts for the treatment of experimental or clinical diabetes. The representative of this journal assures us, however, that it is advisable to refresh the memories of the students of the University of Toronto by brief references to some of the earlier work in this field.

Previous to the year 1889 several investigators had suggested a connection between the pancreas and the disease, diabetes. In that year von Mering and Minkowski proved very conclusively that the complete removal of the pancreas from dogs and other animals resulted in the production of very marked diabetes.

In the year 1869, Paul Langerhans had described those cell groups in the pancreas which are now called the Islands of Langerhans.

Lepine was the first to suggest that the pancreas furnished an internal secretion necessary for the proper metabolism of sugars and fats. Diamare, Shaffer and others have suggested that the islands are the seat of production of the internal secretion of the pancreas. D'Arnozan and Vaieard, Sscobolew, W. G. MacCallum, and others, have shown that the ligation of the ducts of the pancreas results in the degeneration of the acinous cells which produce pancreatic juice, but that the islet cells remain undisturbed by this procedure.

Since the work of von Mering and Minkowski, hundreds of investigators have attempted to prepare from the pancreas a substance which when administered to diabetic animals would alleviate the symptoms of diabetes. Among these investigators the names of Zuelzer, Scott, Rennie, Murlin and Kramer, Kleiner, Clark, Knowlton and Starling, and Paul-esco are prominent. Zuelzer and Scott worked on the hypothesis which was later independently formulated by one of us (F. G. B.). Zuelzer prepared alcoholic extracts of pancreas and administered them to dogs made glucosuric by the injection of epinephrine. He obtained encouraging results for a time but his research was later abandoned. Scott attempted to ligate the pancreatic ducts of dogs but his operations were not successful. He also unsuccessfully attempted to extract the glands with alcohol and we now know that the concentrations he used are unfavorable for the extraction of insulin. Kleiner's experiments with watery extracts of normal dogs' pancreas deserve mention. He obtained some slightly beneficial effects by the administration of these extracts to dia-

betic dogs. His results were not conclusive, however, and his work was not continued.

In 1921 authorities were agreed that all attempts to demonstrate the internal secretion of the pancreas had met with either negative or inconclusive results.

The hypothesis upon which our experiments were founded was that some constituent of the external secretion of the pancreas was antagonistic to the hypothetical internal secretion for which Professor Shaffer of the University of Edinburgh had suggested the name "Insuline". This hypothesis was presented to Professor Macleod of this University and he was able to provide advice and facilities for putting it to the test. Work was commenced in the Department of Physiology on May 16th, 1921. It was originally supposed that only some six or eight weeks would be necessary to test the hypothesis.

In order to eliminate the external secretion of the pancreas it was proposed to take advantage of the above mentioned fact that the acinous cells degenerate after the ligation of the pancreatic ducts. Our first work was therefore to ligate the pancreatic ducts of a number of normal dogs. The animals recovered quickly from the operation and none of them showed any symptoms or signs of diabetes. In the interval required to secure degeneration of the pancreas, we obtained records on totally depancreatized dogs which we contemplated using as test objects. The extreme heat of the summer of 1921 made it very difficult for us to keep the diabetic animals in reasonably good condition and we were not in a position to test any material until late in July.

On July 27th, we decided to make our first test. We anaesthetized a dog whose pancreatic ducts had been ligated some ten weeks previously and removed the degenerated pancreas. The gland was smaller than normal and very firm in consistency. It was immediately sliced into a chilled mortar containing Ringer's solution and the mixture was frozen. After several hours the frozen material was allowed to thaw slowly and the tissue was finely macerated with sand and a pestle. The liquid was then strained off and filtered through paper. This filtrate was the original pancreatic extract used in our experiments. This material was administered by intravenous injection to a diabetic dog. The material exerted a slightly favorable effect upon the blood sugar and sugar excretion of the animal. This experiment was not at all conclusive but extremely encouraging to us, and we made haste to repeat it. Subsequent experiments were very successful and we consistently observed that the administration of this extract of degenerated pancreas resulted in the marked lowering of blood sugar, the diminution of sugar excretion, and phenomenal improvement in the general condition of completely diabetic dogs. The administration of a single large dose of this material often changed a listless semi-comatose diabetic dog into a bright, active animal. Visitors to our working quarters during the months of August and September were greatly impressed with the remarkable effects of this extract. Professor C. L. Starr and Dr. George Young were among the first to witness a demonstration of the beneficial effects of the extract containing the long-sought-for internal secretion of the pancreas. The kindly interest and help of Prof. Henderson was of inestimable value at this stage.

We then proceeded to secure more information concerning the pro-

perties of the extract and its effects upon diabetic animals. It was found that sugar given with the extract was retained to a much greater extent than was the case when it was administered in the absence of the extract. Incubation of the extract with pancreatic juice resulted in the complete destruction of the active material.

When Professor Macleod returned from Europe in September he observed the effects of the administration of the extract. In view of the great importance of the fundamental observation that the active principle of the extract exerted a definite influence upon the blood sugar and sugar secretion of diabetic animals, he advised us to secure even more results along this line. We did this, and in addition were able to show, among other things, that very active extracts could be prepared from other more readily available sources. Active extracts were prepared from the pancreas of foetal calves, taken at a stage of development before the pancreatic ferments had appeared. Potent extracts from normal adult ox pancreas were also secured. To obtain this latter material we extracted finely divided ox pancreas with acidulated alcohol. We consider this a very important experiment since all large scale methods for the preparation of insulin to-day have the acid alcohol extraction as the first step in the process. It was shown that a completely diabetic dog could be kept alive and healthy for at least 10 weeks by the daily administration of this whole gland extract.

The practical application of these results was very evident and in view of this it was deemed advisable to secure the co-operation of other investigators. This was about the middle of December, 1921. Professor J. B. Collip was invited to participate in the biochemical side of the investigation, and was provided facilities by Professor Fitzgerald and Professor Defries of the Connaught Laboratory. A little later Mr. E. C. Noble, Drs. J. Hepburn and J. K. Latchford began work on Insulin under the direction of Prof. Macleod in the Department of Physiology. The work of this group in the winter of 1921-22 resulted in the demonstration of a number of very important facts. It was ascertained that the administration of insulin enabled a completely diabetic dog to store large amounts of glycogen in its liver. It will be remembered that diabetic animals are unable to store greater than 2 per cent. of glycogen in the liver in the absence of insulin even when very large quantities of sugar are administered. It was found that the respiratory quotient of diabetic dogs could be definitely raised by the administration of carbohydrate and insulin. This experiment proved conclusively that insulin caused the burning of carbohydrate in the diabetic organism. The extracts used in the first experiments in which glycogen was found in the livers of completely de-pancreatized dogs and in some of the respiratory quotient experiments, were prepared from adult ox pancreas by our original method. This group also recognized the deleterious effects of overdoses of insulin and discovered that sugar was a very efficient antidote. The effects of insulin upon various forms of experimental hyperglycaemia were studied, particularly by Mr. E. C. Noble. Drs. Hepburn and Latchford showed that the presence of insulin resulted in the increased consumption of sugar by the perfused mammalian heart.

The first insulin administered to diabetic patients in the Toronto General Hospital was prepared from normal ox pancreas by the original

method. This material exerted a definite effect upon the blood sugar and sugar excretion of a diabetic patient. Certain objectionable effects, however, were observed, which were undoubtedly due to the large percentage of protein which this extract contained.

Professor Collip with the knowledge of the properties of the material which we had obtained and with some additional information which he secured by very extensive work, was able in a very short time to purify the original extract so that much of the objectionable inert material was eliminated. The results of the short study of the clinical effects of this material were reported by Drs. Campbell and Fletcher of the Toronto General Hospital, in collaboration with Professor Collip and ourselves.

It will not be possible, in the space at our disposal, to review in detail the various modifications and improvements which have been introduced in the methods of preparation of insulin. A brief summary of some of the more important contributions is submitted. Insulin was originally prepared from the ox pancreas, as stated above, by the extraction of fresh glands with faintly acid alcohol. The concentration of alcohol in our original experiments varied from 40 to 60 per cent. The alcoholic solution of pancreas was filtered and the filtrate concentrated by evaporation of the alcohol and water in a warm air current. Lipoid material was removed by extracting the residue with toluene or ether. The resulting product was the original whole gland extract. We were able to show that the active material contained in this extract was practically insoluble in 95 per cent. alcohol. Professor Collip used acid alcohol as the initial extractive but raised the concentration to about 80 per cent. By this means certain inert objectionable materials were removed. The inert materials were filtered off and the insulin precipitated from the alcoholic solution by raising the concentration of alcohol to approximately 92 per cent. The precipitated material was dissolved in distilled water. Certain difficulties were encountered when it was attempted to apply this method to a larger scale production and various modifications were introduced by the workers in the Connaught Laboratories in the spring of 1922. It was found that the final product obtained by these methods was not sufficiently pure for prolonged clinical use, and efforts were made to secure a better product. The benzoic acid method of Moloney and Findlay which depends upon the fact that insulin is absorbed from watery solution by benzoic acid was successfully used in the Connaught Laboratories for several months. Professor Shaffer of Washington University, St. Louis, and his collaborators, Somogyi and Doisy, introduced a method of purification which is known as the isoelectric process. This method depends upon the fact that if a watery solution of insulin is adjusted to approximately $\text{PH } 5$ a precipitate settles out which contains much of the potent material and relatively few impurities. Dudley has found that insulin is precipitated from watery solutions by picric acid and he has made use of this fact to devise a very ingenious method for the purification of the active material. Mr. D. A. Scott, and one of us (C. H. B.), who are responsible for the preparation of insulin in the Insulin Division of the Connaught Laboratories, have tested all the available methods and have appropriated certain details from many of these. Several new procedures which we believe are advantageous have also been introduced. The method of preparation of insulin which may be seen in operation at any time in the Insulin Division, is as follows:—

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The beef or pork pancreas is finely minced in a large grinder and the minced material is then treated with 5 c.c. of concentrated sulphuric acid, appropriately diluted, per pound of glands. The mixture is stirred for a period of three or four hours and 95 per cent. alcohol is added until the concentration of alcohol is 60 to 70 per cent. Two extractions of the glands are made. The solid material is then partially removed by centrifuging the mixture and the solution is further clarified by filtering through paper. The clear filtrate is concentrated in vacuo to about 1/20th of its original volume. Ammonium sulphate (37 gms. per 100 c.c) is then added to the concentrate and a protein material containing all the insulin floats to the top of the liquid. The solid material is skimmed off and dissolved in water. Certain inert materials are eliminated by adding alcohol to this watery solution so that the concentration of alcohol is approximately 80 per cent. An equal volume of ether is then added to the 80 per cent. alcohol and the precipitate which forms contains practically all the potency which was present in the alcoholic solution. The solution of this precipitate in water is adjusted to approximately PH 5 and a white flocculent precipitate settles out. The solution of this latter precipitate in acid water (PH 2.5) is the final product as it is distributed at the present time.

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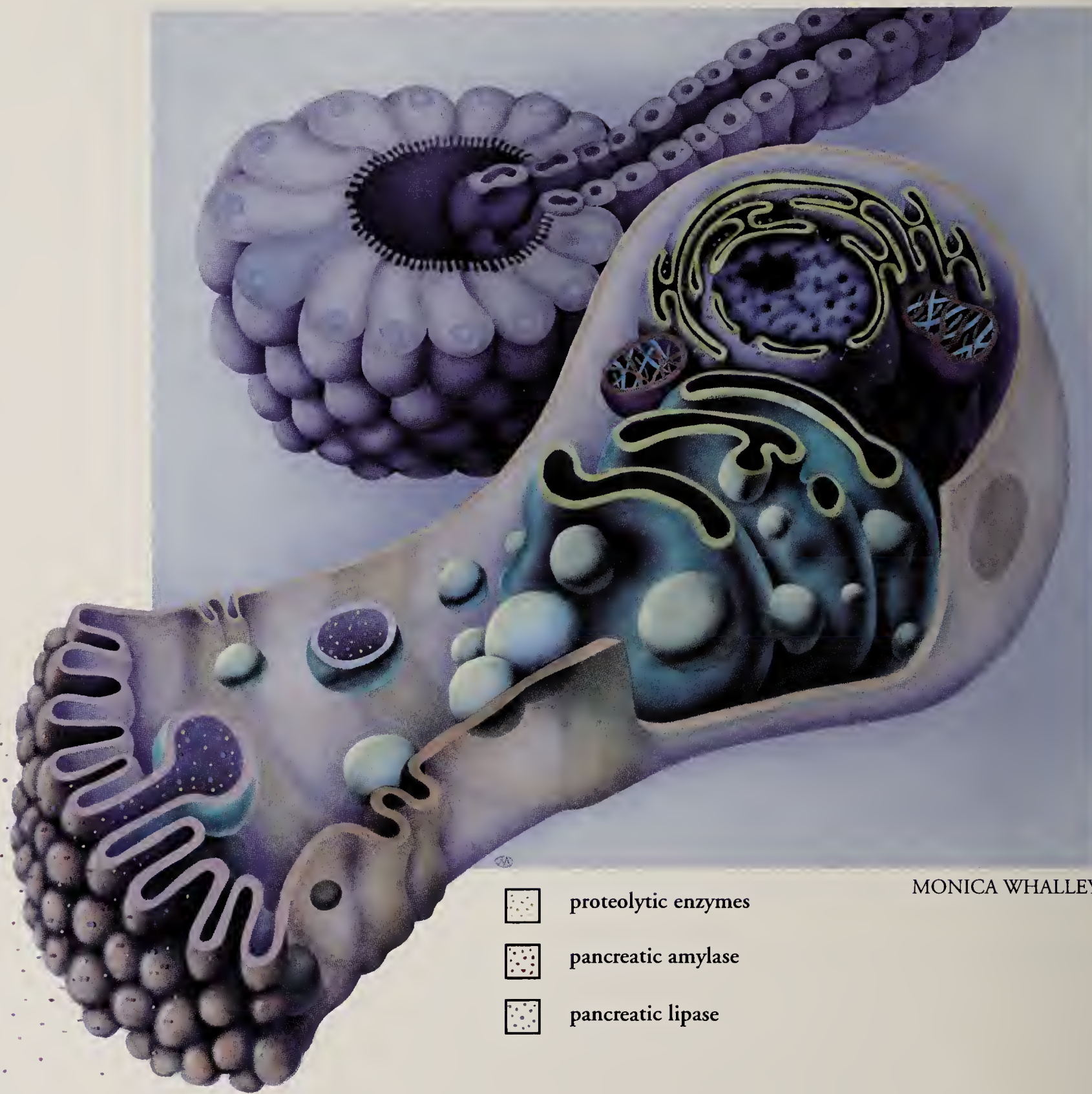
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